Title: Alzheimer's disease as a syndrome of overloaded amyloidic synaptic tagging in memory networks

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Highlights:

- A hypothetical model of the role of amyloid beta and tau phosphorylation in Alzheimer's disease is presented
- Aggregation of amyloid beta is proposed to write-protect plasticity underlying memory
- Buildup of phospho-tau is proposed to form an image of established plasticity as insurance against plasticity-threatening insults
- Alzheimer's disease is postulated to be a syndrome caused by overloading of memory circuits resulting in aggregated amyloid beta reaching neurotoxic levels
- Isodendritic neuromodulators such as norepinephrine and acetylcholine governing sleep and cognitive processing are postulated as controlling memory and delivering tau forms for imaging the potentiation state of synapses.

Declarations of interest: none

Important: *This article is provided as a working hypothesis that has not been peer-reviewed. The article should not be regarded as irrefutable, guide preclinical study or clinical practice/health-related behavior, or be reported in news media as established information.*

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Abstract:

Alzheimer's Disease is defined as progressive memory loss coincident with accumulation of aggregated amyloid beta and phosphorylated tau. Identifying the relationship between these features has guided Alzheimer's Disease research for decades, principally with the view that aggregated proteins drive a neurodegenerative process. Here I propose that amyloid beta and phospho-tau write-protect and tag neuroplastic changes as they form, protecting and insuring established neuroplasticity from corruption. In way of illustration, binding of oligomeric amyloid beta to the prion receptor is presented as an example possible mechanism. The write-protecting process is conjectured to occur at least partially under the governance of isodendritic neuromodulators such as norepinephrine and acetylcholine. Coincident with aging, animals are exposed to accumulating amounts of memorable information. Compounded with recent increases in life expectancy and exposure to information-rich environments this causes aggregating proteins to reach unforeseen toxic levels as mnemonic circuits overload. As the brain cannot purposefully delete memories nor protect against overaccumulation of aggregating proteins, the result is catastrophic breakdown on cellular and network levels causing memory loss.

Keywords:

Alzheimer disease, amyloid beta, tau, memory, prion protein, neuronal plasticity, nerve degeneration, norepinephrine, acetylcholine, synapses, sleep

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1. Introduction

Alzheimer's Disease (AD) is the most common cause of dementia, representing about 60 to 70% of cases. Among its known risk factors, age is usually cited as the most substantial. Around 4% of AD cases are of the early onset type, usually affecting people in their 40s to early 60s. Early onset AD, known also as familial AD (FAD), is believed to be driven by mutations in genes directly related to the classically understood pathology of AD – buildup of aggregated amyloid beta ($A\beta$). The remainder of cases, are of the late onset (LOAD) or sporadic type. The etiology of LOAD is less clear and far more loosely genetically linked despite the pathology and symptomology of FAD and LOAD being similar.

The statistics surrounding AD are alarming and need little introduction. In 2018, dementia was the most common cause of death on UK death certificates of which AD constituted about a third of cases. Only pooled cases of cancer eclipse this disturbing statistic. In the US, about one in three seniors die of AD or another form of dementia. Current estimates suggest that by the age of 65, 1 in 10 people are clinically diagnosable as AD dementia with probably more going undiagnosed. By 85 years of age, the likelihood of receiving a diagnosis of AD is somewhere between a staggering one in two to one in three. For context, the WHO reported mean life expectancy worldwide in 2019 as 72.6 years. The emotional and financial toll on sufferers, caregivers and healthcare systems is enormous. As aged populations increase, the incidence of AD is predicted to increase accordingly. Yet, of the top 10 causes of death, AD is alone without any method for preventing, curing, or slowing progression.

1.1. The $A\beta$ cascade hypothesis

Histologically, the most salient features of AD are synaptic loss, buildup of extracellular aggregates of $A\beta$ and intracellular aggregates of phosphorylated forms of the microtubule-associated protein tau (pTau) (Serrano-Pozo et al., 2011). One of the earliest and most influential hypotheses devised to explain the etiology of the disease is the " $A\beta$ cascade" hypothesis (see Hardy and Allsop, 1991; Hardy and Higgins, 1992; Selkoe, 1991). This hypothesis, held by what are colloquially known as β abstists, originally positioned accrual of $A\beta$ aggregates as driving the disease. Despite increasing concerns over the hypothesis' validity (e.g. Castellani and Smith, 2011; Chetelat, 2013; Hardy and Mayer, 2011; Harrison and Owen, 2016; Kametani and Hasegawa, 2018; Makin, 2018; Marchesi, 2012; Morris et al., 2018; Saxena, 2010), often roused by the failure of the hypothesis to deliver a successful treatment, that $A\beta$ could be the *primum movens* is supported by substantial evidence (e.g., Carrillo-Mora et al., 2014; Harrison and Owen, 2016; Lee et al., 2017a; Leong et al., 2020; Palop and Mucke, 2010; Reiss et al., 2018; Sadigh-Eteghad et al., 2015; Selkoe and Hardy, 2016; Smith and Strittmatter, 2017; Verdile et al., 2004; Viola and Klein, 2015). Most notably $A\beta$ plaques are a major histological feature of (and define) the disease, oligomeric $A\beta$ (o $A\beta$) levels increase in AD, gene mutations affecting production and aggregation of $A\beta$ occur in FAD and not least, extensive preclinical research showing toxic potential of $A\beta$. Furthermore, polymorphisms in genes, particularly apolipoprotein E (ApoE), involved in $A\beta$ clearance are associated with LOAD.

This is not to say that the hypothesis is free of issues. For instance, some have suggested $A\beta$ accumulation is not the cause of AD, particularly LOAD, but a response (Castello and Soriano, 2014; Panza et al., 2019b; Petrofes Chapa et al., 2012; Struble et al., 2010). Issues include inconsistencies between the spatiotemporal deposition of $A\beta$ and the progress of cognitive symptoms, criticisms of preclinical experimental approaches and ambiguity over the exact toxic species of $A\beta$. Unsurprisingly, the amyloid cascade hypothesis has come under increasing fire with some going as far as suggesting it has been misleading and pursuing it a sunk-cost fallacy (Amtul, 2016; Castellani and Smith, 2011; Castello and Soriano, 2014; 2011).

Nonetheless, for better or worse, the amyloid cascade hypothesis has undoubtedly been very influential, forming the basis of a large field of research and clinical development. In fact, by 2009 of the top 10 most cited authors in the AD field, the main area of investigation of four of them was A β or A β production (Sorensen, 2009). Three of the 10 focused on tau. The original conceptualization of the amyloid cascade hypothesis positioned large extracellular A β plaques as causing cognitive and behavioral changes. However, as time has passed it has become apparent that A β plaques correlate poorly with disease symptoms. This yielded a revised version of the hypothesis whereby much smaller aggregates of A β , particularly oligomers of the 42 amino acid isoform (oA β ₄₂) are believed to be the primary cause (Cline et al., 2018). Among evidence supporting this revision are studies showing buildup of oA β during the disease (see Ferreira et al., 2015; Kaye et al., 2003), stronger correlation of oA β with cognitive deficits in mouse models and oA β being more neurotoxic (Ferreira et al., 2015). The sheer magnitude and influence of the amyloid cascade hypothesis cannot be understated. It has funneled immense amounts of research funding and efforts in its direction, often motivated by demonstrating the toxicity of A β . This has not only come at the expense of seeking other explanations but has arguably induced an inherent bias in data available upon which alternative explanations can be built. Nonetheless, accumulation of A β remains far more than a straw in the wind and as such requires explanation.

1.2. The case for tau

For various reasons including some of those mentioned above, attention has shifted away from A β to the other key histological feature of AD: hyperphosphorylated tau, tau aggregates and neurofibrillary tangles (NFTs) (Iqbal et al., 2016). Evidence suggesting that intracellular accrual of pTau drives neurodegeneration (a view held by what are colloquially known as Tauists) is indeed sizable with tau tangle pathology preceding formation of A β plaques as being particularly compelling (see Kametani and Hasegawa, 2018). Oft cited, brain distribution of tau pathology better predicts progression of the disease, synaptic breakdown and cognitive deficits (Brier et al., 2016; La Joie et al., 2020). Along with studies showing A β -induced hyperphosphorylation and aggregation of tau and the fact that there exist several other tauopathies absent of major A β pathology make it easy to envisage A β could drive pathology by recruiting tau (Bloom, 2014; He et al., 2018; Musiek and Holtzman, 2015). To some degree this too is a credible hypothesis. Not least because pTau can be toxic (Bretteville and Planell, 2008; Cowan and Mudher, 2013; Gotz et al., 2008) but also because mutations in the tau encoding gene MAPT are conspicuously absent in AD. Furthermore, A β plaques can be found in the absence of neurodegeneration but NFTs are found in frontotemporal dementia and other tauopathies. That said, experimental anti-tau therapies have still to meet major success in clinical trial (Congdon and Sigurdsson, 2018; Medina, 2018).

In the understandable rush to develop treatment strategies most interest has been in understanding pathological effects of A β and pTau. However, as has been repeatedly pointed out, amyloid precursor protein (APP), the precursor from which A β is cleaved and tau *do* have important dose-dependent physiological roles (e.g. Avila et al., 2004; Brothers et al., 2018; Crdenas-Aguayo et al., 2014; Dawkins and Small, 2014; Guo et al., 2012; Kent et al., 2020; Ludewig and Korte, 2016; Morley and Farr, 2012; Muller et al., 2017; Puzzo et al., 2015a; Regan et al., 2017; Sotiropoulos et al., 2017). An increasing voice of opinion emphasizes that understanding these roles will not only help understand the etiology of AD and other dementias and develop effective interventions, but could protect against inadvertently worsening dementias by inappropriately interfering with A β and tau physiology (Castello and Soriano, 2014; Giuffrida et al., 2009; Kent et al., 2020; Puzzo, 2019; Puzzo et al., 2015a).

1.3. A β and tau aggregation as molecular tags of persistent memory

There is increasing recognition that protein aggregation is not simply an aberration of nature. So-called “functional amyloids” are found in multiple mammalian systems (see Rubel et al., 2020; Stroo et al., 2017). Here I outline a hypothesis aiming to explain how the two major hallmarks of AD – accumulation of A β and pTau – relate to normal mnemonic and cognitive processes and pathology. Recognizing these roles may require reconsidering or re-interpreting some experimental findings to date. However, this certainly does not necessarily negate progress made so far. Central to the hypothesis is the prediction that aging *per se* is not the primary cause of AD. Rather, accumulation of experiences and memories that *accompany* aging is the culprit. I present evidence that A β and tau may play key roles in protecting and marking (tagging) memories for long-term storage. As individuals age, inevitable accumulation of experiences exceeds the ability to store them. This causes A β and tau aggregates to reach pathological levels ultimately inducing catastrophic collapse of brain function. I reason that the problem is compounded by the brain’s inability to deliberately purge itself of un-needed plasticity and memories. I forward that this is at least partially due to a relatively sudden increase in lifespan exacerbated by, but independent from, massive increases in exposure to memorable information.

At this point, it is important to recognize that aggregated A β and NFTs may by no means be the *only* factors driving AD, if they drive it at all (see Garrett, 2018). More important factors may already be known but not recognized or awaiting discovery. Nonetheless, given the immense influence of A β and pTau on the field, they warrant particular consideration. As will be covered, there is intense interest in understanding interactions between the two. However, here they will initially be discussed separately before considering their interaction. Given the immense body of studies published on AD alone, I will refer extensively to review articles, citing particularly relevant or recent primary studies as appropriate. Regrettably, for the sake of brevity, many aspects of the disease will not be covered though I endeavor to provide a degree of contextual information for those less familiar with this diverse field. This is not to say they are unimportant or unsuitable targets for therapeutic intervention. However, I wish to retain focus on what in the author’s opinion could be the cause of AD.

2. Synaptic tagging and long-term memory storage

Surviving and thriving in an environment requires acquiring long lasting and modifiable memories. The most widely accepted neuropsychological model of memory formation is based on changing efficacy in synaptic connectivity to generate physical representations known as “engrams” or memory traces. Such neuroplasticity is likely found between most, if not all neurons underpinning all forms of memories, be they implicit or explicit. By strengthening or weakening the ability of neurons to excite connected neurons, memories are stored, strengthened, weakened, modified and extinguished across synapses distributed over whole networks.

Functionally, neurons are believed to strengthen and weaken connections through the processes of long-term potentiation (LTP) and long-term depression (LTD) respectively. These processes are considered key to acquisition, consolidation, reconsolidation and extinction of memories, and likely forgetting. The molecular and genetic underpinnings of these processes, along with related molecular processes such as synaptic facilitation, depotentiation, synaptic scaling and metaplasticity have been the focus of intense study. Here they will not be reviewed in detail (see Korte and Schmitz, 2016) but in essence, modifications in the expression and trafficking of AMPA receptors (AMPA) and NMDA receptors (NMDARs) lie at the heart of changes in the synaptic strength at excitatory synapses. Changes

that rely on multiple intracellular and extracellular signaling events and long-term changes in gene expression.

2.1. Establishment of long-term memories

Appropriately and permanently integrating localized changes in plasticity into already established engrams requires the brain to carefully determine where they appropriately belong. This determination is very difficult to make on the fly, particularly when what is to be potentially remembered long-term may not yet be fully comprehended or is still being elaborated. In way of analogy, imagine if one were presented the task of remembering a chess set. Is the memory best associated with black and white objects such as cats and barcodes, royal families, chequered patterns, board games, or any of many other possibilities? This determination requires referencing not only established engrams held in long-term memory, but those recently acquired and held in short term memory. Furthermore, this referencing is not just a matter of identifying likenesses but requires deep abstraction. This process appears to be coordinated from the hippocampus requiring the brain to go “offline” while potential new longer-term memories are appropriately consolidated (Rasch and Born, 2013). As will be discussed, it is mostly during sleep that new information is sorted and selected for permanent storage. Information deemed of lesser value (for example, what you ate for breakfast last Monday morning) is ultimately forgotten though whether or not this is an active or passive process is not fully understood.

The “stamping in” of longer-term memories relies largely on repetition and their emotional salience (Bergado et al., 2011; Dunsmoor et al., 2015), the latter particularly being controlled and attributed by isodendritic neuromodulators such as norepinephrine (NE), dopamine and serotonin. Rote learning of emotionally-bland information (such as telephone numbers) is possible through deliberate rehearsal but many memories are acquired through positive and negative reinforcement mechanisms relying on rewards and punishers. These memories are associated with events that elicit strong emotional reactions such as fear, pleasure, terror or surprise and can be learned with little reinforcement or effort. In extreme cases profoundly long-term, resilient and sometimes troublesome memories, often termed “flashbulb” memories (e.g., where one was when they heard of the 9/11 attacks, the moment of a child being born) can be stamped in instantly and indelibly for lifelong storage.

A particularly important question is how are changes in synaptic strength maintained over very long periods? What prevents new neuroplasticity interfering with or corrupting already established plasticity? That is, for a memory system to function correctly, engrams must be laid out in a highly organized manner that ensures their permanence, accessibility, modifiability and interconnectedness as new memories are incorporated. Changes in synaptic efficacy are often viewed in stages ranging from seconds to years. The specific question of interest here is, how can memories last from hours to a lifetime? One method by which this is postulated to occur is through the process of synaptic tagging and capture (STC) (Frey and Morris, 1997; Martin and Kosik, 2002; Moncada et al., 2015; Redondo and Morris, 2011). According to the STC hypothesis, the fate of a memory is not established at its induction but rather by generation of a “tagged” state that can occur independent of LTP (Redondo and Morris, 2011). This tagging occurs only at synapses that have undergone changes in synaptic efficacy and is hypothesized to provide the basis for establishing very long-term memories¹.

¹ A major issue to the field is defining and distinguishing short from long-term memories. Generally, the field views any memory that persists beyond a few minutes as long-term, usually equated with changes in gene expression (Dudai, 2002). Though here I generally follow this same nomenclature for the sake of consistency, it is important to stress that the type of long-term memories that I propose that aggregating proteins tag and protect are those

2.2. Plasticity related products

Precisely what and how molecules, known as plasticity-related products (PRPs), tag memories for long-term storage is still not fully resolved. A bona fide PRP molecule must meet a specific set of criteria. These include localization to the point of the plastic change, being limited in time, being reversible and able to produce long-term changes in efficacy at specific synapses (Martin and Kosik, 2002). Long-lasting changes in synaptic efficacy depend on reorganization of pre-synaptic and post-synaptic molecular networks that include molecules such as AMPARs, NMDARs, metabotropic receptors (mGluRs), cAMP, Ca^{2+} ions, protein kinase A (PKA), protein kinase C (PKC), calmodulin, calcineurin, Ca^{2+} /calmodulin-dependent protein kinase II (CaMKII) and cAMP response element-binding protein (CREB) to name just some of the better understood (Kandel et al., 2014; Korte and Schmitz, 2016). Reorganization of molecular networks include not only alterations in turnover of local molecules and post-translational modifications such as phosphorylation, but permeate to the transcriptional and translational level. Though these molecules are highly instrumental in altering plasticity, PRPs are distinguished by their ability to ensure that the reorganization of molecular networks underlying memory are *maintained* and *protected* over relatively very long terms. This functions to mark the recruitment of neuroplastic changes into engramic circuits but also guards against events that threaten to undo these changes. As such, STC locks-in modifications in synaptic efficacy, possibly acting as linchpins in molecular networks. Though this field is nascent, the production and maintenance of synaptic tags is controlled by many intracellular and extracellular events governing wider changes in network connectivity and memory formation. These include sensitivity to neuromodulators of learning such as dopamine (Moncada et al., 2011; Navakkode, 2015; Sajikumar and Frey, 2004; Wang et al., 2010b) and NE (Moncada et al., 2011), (see Palacios-Filardo and Mellor, 2019; Rombouts et al., 2015).

Several molecules have been forwarded as candidate PRPs (summarized in **Table 1**). These include brain-derived neurotrophic factor (BDNF), protein kinase M ζ (PKM ζ), activity-regulated cytoskeleton-associated protein (Arc), Homer1a, AMPAR type subunit 1 (GluA1) and dendritic RNAs (see Martin and Kosik, 2002; Moncada et al., 2015; Okuda et al., 2020; Rogerson et al., 2014). As convenient as it would be, it is unlikely that any one single molecule acts alone in STC or even that common mechanisms exist from brain region to brain region. Tagging mechanisms such as phosphorylation/dephosphorylation events are very widespread in biological systems and the concept that switching chemical states of a molecule underlies a long-term change in synaptic efficacy is a well-accepted postulate. For instance, CREB, a molecule long understood as central to LTP is regulated by phosphorylation. CaMKII, which also has a central role in maintaining LTP, is also regulated by phosphorylation and is capable of autophosphorylation hypothesized as forming a molecular basis of long-term memory (Lisman, 1994). For example, through its ability to autophosphorylate, the atypical protein kinase PKM ζ can sustain long-term synaptic changes (see Sacktor, 2011; Sacktor, 2012). Additionally, recruitment of dendritic RNAs by PRPs likely underlie a sub-program of protein translation events key to solidifying local changes in plasticity (Doyle and Kiebler, 2011).

Most if not all candidate PRPs are well-established as having central roles in modulating synaptic efficacy. For example, Arc regulates numerous processes central to synaptic stability such as cytoskeletal structure, AMPAR trafficking and gene transcription (Nikolaenko et al., 2018). Interestingly, as will be discussed below (see sections 8.1, 17), in vitro studies suggest Arc can undergo reversible self-oligomerization (Myrum et al., 2015) and trans-synaptic spread (Pastuzyn et al., 2018); properties that

maintained over hours to years and as such will refer to them as “longer-term”, “very long-term” or “lifelong” memories.

might be fundamental to some PRPs. Whether or not the same PRPs are responsible for different types (e.g., LTP versus LTD), aspects (e.g., functional versus structural) or phases (e.g., consolidation versus reconsolidation) of the plasticity process is an area of ongoing study.

3. Aggregating proteins as solid-state synaptic tags

A striking commonality between the most common age-related dementias is the presence of so-called misfolded and aggregated proteins (Lovestone and McLoughlin, 2002). Currently, aggregated proteins such as A β , α -synuclein (α -syn), Huntingtin, TAR DNA binding protein (TDP-43), superoxide dismutase 1 (SOD1), transthyretin, prion protein and tau are associated with over 30 different neurodegenerative diseases. Though it is becoming increasingly clear that no single one of these associates uniquely with any one neurodegenerative disease (though this may be in large part a result of how the diseases are defined, see Garrett, 2018), there is clearly a strong preponderance for particular aggregating proteins, or combinations thereof, to associate with particular diseases and symptomologies. Importantly, and has often been raised as an argument against the credibility of the amyloid cascade hypothesis, many of these proteins build up and aggregate in the brains of apparently healthy individuals showing no cognitive deficits. This has led to the notion that prior to exhibiting overt cognitive deficits, many age-related dementias pass through a prodromal stage where cognitive deficits go unnoticed or are passed off as so-called age-related cognitive decline (or normal cognitive aging). As I will elaborate, and as others have argued (Nehls, 2016) though many of these changes are technically “age-related”, it is not aging per se that drives them.

3.1. Prion protein and prion-like proteins

Aggregating proteins share several important features: ability to (1) self-template, i.e., aggregate, (2) “seed” aggregation in like and different proteins, (3) exhibit extreme stability and protease-resistance, (4) spread trans-synaptically through neuronal circuits, and (5) induce neurotoxicity and provoke other inflammatory and immune responses. It is these features and their resemblance to prion protein that have led to them often being termed “prion-like”. Prion protein, upon which the prion field was founded and the word “prion” coined is the archetypical prion. Often referred to as Prp, prion protein exists either in its normal monomeric non-aggregated soluble or membrane-bound form known as cellular prion protein (PRPC), or in a protease-resistance aggregated form known as PRPSc. This latter form is highly neurotoxic and causes the neurodegeneration found in a handful of very rare but devastating neurodegenerative diseases including Creutzfeldt-Jakob disease (CJD), kuru and bovine spongiform encephalopathy (known also as mad cow disease). Particularly remarkable is that Prp is a highly “infectious” protein that can spread from cell to cell within the same organism and between organisms of different species (Si, 2015; Takada and Geschwind, 2013). It is no surprise that the obvious similarity in the ability of “prion-like” proteins such as A β , tau and α -syn aggregate, to pass between cells in a process known as “prion-like spread” (see section 18) and wreak destruction on the nervous system in a manner similar to PRPSc has led them to be generally viewed in a negative light².

² It may be useful to newcomers to clarify what might be confusing nomenclature and terminology. The term “prion” (a portmanteau derived from “protein and infection”) refers to any misfolding protein able to pass their misfolded shape onto what are assumedly normal variants of the same protein - a process called “self-templating” or “seeding”. “Prion protein”, known also as “PrP”, is a *particular* 36 kDa protein that causes the transmissible neurodegenerative disease Creutzfeldt-Jakob disease (among others) from an increasing list of known prion proteins. Because its discovery founded the prion field, it was conferred what now appears to be the generic name of “prion protein” though in fact it is a specific highly conserved mammalian protein encoded by the PRNP gene.

Conventionally, prions and prion-like proteins are viewed as existing in at least two states: as single molecules (monomers) or as larger aggregated (i.e. amyloidic) oligomers of two or more monomers (Si, 2015). Though this distinction is useful for understanding their physiological and pathological properties on a basic level, it is probably more useful to view prion-like proteins as existing over a range of sizes determined by how many monomers are incorporated into the aggregate. These different sized aggregates are often named based on their presentation, e.g., oligomers, fibrils, plaques, inclusions and filaments. Though the term prion has become virtually synonymous with a protein with malicious intentions, not all prions are in fact bad or the result of a pathological mishap. Rather, some aggregating proteins termed “functional prions” serve important physiological and beneficial functions (Rayman and Kandel, 2017). The archetypal examples of such functional prions are yeast prions that constitute *heritable* epigenetic elements encoding information of adaptive value passed from generation to generation by “infecting” offspring (Liebman and Chernoff, 2012; Wickner et al., 2015). For example, the yeast prion protein URE3 represses transcription of genes matching nitrogen catabolism to availability of nitrogen sources. In this sense, yeast prions act essentially as genes, or stores of information (An et al., 2016), albeit that the information encoded is far more rudimentary than that by nucleic acids (see Liebman and Chernoff, 2012). Importantly, by interconverting between monomeric and oligomeric forms prions act as protease-resistant solid-state molecular switches toggling cells between different physiological states.

3.2. CPEB: an example of a prion-like protein subserving persistence of long-term memory

The notion that proteins could encode stored information is by no means new. Based on their permanence, Crick postulated in the 80s that molecules forming dimers and modification by phosphorylation could function as substrates for long-term memory (Crick, 1984). More recently, Tompa and Friedrich suggested prions could act as bistable molecular switches conferring stable phenotypes, citing memory as one possibility (Tompa and Friedrich, 1998). Recent studies support the notion that proteins can encode long-term changes in neuroplasticity. Working in the nervous system searching for PRPs of the marine snail *Aplysia*, the Kandel group discovered a self-aggregating protein with functional properties in the nervous system. This protein, known as cytoplasmic poly-adenylation element-binding protein (CPEB) was first identified in *Xenopus* oocytes where it functions as a translational regulator activating dormant mRNAs (Hake and Richter, 1994). Synaptic stimulation with serotonin increases a neuronal isoform of CPEB (known as ApCPEB) only in stimulated synapses. ApCPEB exists in at least two conformational states, either monomerically where it is either inactive or represses translation, or a

“PrP-C” (referred to here as PRPC), which is the *non-pathogenic* unaggregated form of prion protein is expressed throughout the body but predominately in nervous tissue where it forms a cellular glycosyl-phosphatidylinositol-anchored protein capable of binding other molecules and inducing cellular responses. In this sense, PRPC acts as a cell surface receptor (though cleavage from the membrane can also produce soluble forms) and thus it is often referred to as the “prion receptor”. The precise physiological function and reason for the existence of prion protein, either as a receptor or in some other capacity, has been a matter of ongoing research (see Aguzzi et al., 2008; Castle and Gill, 2017; Wulf et al., 2017). Among the molecules that prion protein binds are several *other* aggregating proteins, such as A β and α -syn, some of which too are found in neurodegenerative diseases. Because, like prion protein itself, these proteins can aggregate and self-template they are often referred to simply as “prions” or “prion-like”. “Amyloids” are aggregates of proteins, usually with a fibrillar morphology, and though they are generally associated with diseases called amyloidosis, are occasionally found serving beneficial functions, such as storing peptide hormones in secretory granules. Thus, aggregated proteins are amyloids, all prions are amyloids, but not all amyloids are considered prions. Whether or not the binding of prion-like proteins to prion protein has a purposeful physiological function or is a pathological accident is unclear, but is a question central to the current discussion.

multimeric self-perpetuating prion-like state that activates dormant mRNAs local only to stimulated synapses. The latter state contributes to a self-sustaining long-term molecular change that stabilizes learning-related synaptic modifications thereby promoting memory storage (Si et al., 2003). The *Drosophila* homologue of CPEB, Orb2, serves a similar function of stabilizing activity-dependent changes in synaptic efficacy by a similar mechanism. Importantly, the ability of CPEB and Orb2 to self-aggregate in response to physiological signals (rather than spontaneously as appears to be the case of some prions) is key to effecting this change in neuroplasticity (see Si and Kandel, 2016).

A role of CPEB in maintaining long-term memory is not limited to *Aplysia* (see Qu et al., 2020; Si, 2020; Sudhakaran and Ramaswami, 2017). Mice possess four isoforms of CPEB (CPEB1-4) of which CPEB3 has an amino terminal domain most resembling apCPEB (see Si and Kandel, 2016). CPEB1 has established roles in synaptic plasticity (Alarcon et al., 2004; Zearfoss et al., 2008) but only CPEB2 and CPEB3 have aggregation potential. Most studies have focused on CPEB3 revealing findings supporting its role in maintaining long-term memory, including an association with episodic memory in humans (Vogler et al., 2009). Firstly, in its basal state CPEB3 represses translation of target mRNAs relevant to synaptic plasticity including those coding PRP AMPAR subunits GluA1 and GluA2 (Huang et al., 2006; Pavlopoulos et al., 2011). Deletion of CPEB3 enhances short and long-term memory by curbing expression of GluR1 and GluR2 subunits (Chao et al., 2013). Mice with CPEB3 conditionally knocked out of the hippocampus and cortex show impaired memory and LTP and critically this involvement depends on the presence of CPEB3's prion-like amino terminus domain (Fioriti et al., 2015). On neuronal stimulation, CPEB3 levels increase and aggregate (Fioriti et al., 2015) releasing the translation of target genes. These changes depend on post-translational modifications of CPEB3 including SUMOylation, which normally act to maintain CPEB3 in its basal form. The key point here is that by acting as a functional prion, *aggregation* of CPEB3 is important to establishing and maintaining long-term changes in synaptic efficacy. In this way, CPEB3 acts as a solid-state metastable proteinaceous switch resistant to degradation, governing maintenance of long-term memory. Remarkably, recent studies find that blocking aggregation of CPEB3 prevents consolidation of traumatic events in mice (López-García et al., 2020).

However, many questions remain. For instance, how permanent is this synaptic tag? Do mechanisms exist to reverse the tagging process? How is the tag impacted by new attempts to alter plasticity in already tagged cells? To what degree does the extent of aggregation of the tag determine the strength of the tagging? Relative to other aggregating proteins, CPEB3 is very large (76 kDa) presenting many sites for post-translational modification that could modulate propensity to self-aggregate. In comparison, the 42 amino isoform of A β is only 4.5 kDa, α -syn is 14.4 kDa and about 55 to 62 kDa. Could the relatively small size of A β be in keeping with a "releasable" neuromodulator-like molecule similar in size to for example neuropeptide Y (4.3 kDa), orexin (3.6 kDa) and β -endorphin (3.5 kDa) - small enough to be rapidly diffusible but large enough to reliably and controllably aggregate? Either way, that the permanence of memory can fundamentally be determined by the aggregation status of a protein has wide ramifications and as I present here, may be key to understanding many dementias characterized by deposition of protein aggregates.

4. Amyloid beta (A β)

4.1. Metabolism of A β

Given its predicted role in AD, much effort has been directed towards understanding the metabolism of A β . For the sake of brevity, the reader is referred to recent reviews for illustrations and thorough discussion (Dawkins and Small, 2014; Guo et al., 2012; Muller et al., 2017; O'Brien and Wong, 2011).

Here, I will draw attention only to general or particularly pertinent aspects. As A β exists in various isoforms of differing lengths and aggregation configurations, unless otherwise stated I will use the term “A β ” to cover the possibility of any or all of these forms unless otherwise specified.

A β is produced through the cleavage of the membrane bound type 1 receptor amyloid precursor protein (APP) which due to alternative splicing exists as three different isoforms in humans. The 695 amino-acid long isoform of APP (APP695) is abundantly and almost uniquely expressed in neurons whereas the other two other isoforms (APP751 and APP770) are expressed largely in non-neuronal cells. APP695 lacks a Kunitz-like protease inhibitor domain and Ox-2 antigen domain and APP751 lacks only the Ox-2 domain. All isoforms contain the A β domain that spans part of the juxtamembrane and transmembrane domains (Muller et al., 2017). Generally, The APP gene is highly expressed in brain showing little specificity to any particular region.

The catabolism of APP passes along two major canonical lines of processing called the “non-amyloidogenic” and “amyloidogenic pathways”, the latter generating A β . The pathway down which processing occurs depends on whether APP is cleaved first by α -secretase (non-amyloidogenic processing) or β -secretase (amyloidogenic processing). APP is sorted in the endoplasmic reticulum and Golgi apparatus and then directed to the synapse by fast axonal transport. Once inserted into the cell surface in lipid rafts, APP can undergo non-amyloidogenic cleavage by α -secretase (by ADAM family proteases, particularly ADAM10) yielding a soluble extracellular domain called sAPP α . Further cleavage by γ -secretase yields p3, a protein comprised partially of the original transmembrane length of APP, and the intracellular domain termed APP intracellular domain (AICD). During amyloidogenic cleavage the full-length APP sequence first undergoes β -secretase cleavage (largely by β -secretase 1 [BACE1], but also β -secretase 2 [BACE2]) to yield a soluble extracellular domain called sAPP β and a remaining transmembrane domain called C-terminal fragment β (CTF β , also known as C99). Subsequent γ -secretase cleavage liberates various length isoforms of A β from what was partially the transmembrane region of APP, and again AICD. A β has a strong and pathological affinity for membranes, likely due to the fact that part of its sequence originally existed in the transmembrane region (Bharadwaj et al., 2018). The exact length of the liberated A β fragment depends on the site at which γ -secretase makes its cleavage, yielding A β of mostly 40 amino acid length (A β ₄₀) or 42 amino acid length (A β ₄₂) though forms of up to 44 amino acid length may be produced. A β fragments are then released into the extracellular space. Naturally, the precise site of γ -secretase cleavage impacts the length of the remaining AICD fragment that passes into the cell where it is involved in many intracellular signaling functions (Bukhari et al., 2017). A proportion of cell surface APP is also internalized into endosomes though the reason for this is unclear.

About 10% of A β produced is the A β ₄₂ isoform. A β ₄₂ is considerably more aggregation-prone than A β ₄₀ and considered the driving molecule in AD pathology. A β ₄₂ is also heavily implicated in Down’s Syndrome where overproduction occurs due to an extra copy of the APP gene being among the duplicated chromosomes 21 genes. Down’s syndrome patients exhibit A β plaques, NFTs of pTau and often present AD-like dementia around middle age onwards (Head et al., 2012), an observation that lends strong support to the credibility of the A β cascade hypothesis. APP can also undergo various lines of “non-canonical” processing such as by η -secretase or caspase processing yielding various other fragments though none of these known alternative processing pathways yield A β ₄₀ or A β ₄₂. The physiological and/or pathological functions of non-canonical processing is largely unknown (see Muller et al., 2017), though one should certainly be cognizant of them when considering APP function.

4.2. A β in AD

Some of the strongest evidence for the criticality of A β in driving AD derives from natural mutations affecting generation of A β_{42} , particularly those found in APP and γ -secretase coding genes. γ -secretase is comprised of four subunits – presenilin-1 (PSEN1), nicastrin, anterior pharynx defective 1 and presenilin enhancer 2. It is important to note that γ -secretase cleaves not only APP but has over 90 other known targets, some of which are particularly relevant to AD. These include triggering receptor expressed on myeloid cells (TREM2), Notch and structural plasticity-related proteins such as cadherins, β -catenin and integrins.

Over 180 mutations in presenilin genes are associated with early onset, autosomal dominant, fully penetrant AD, the majority of which occur in the PSEN1 gene. Over 30 mutations in APP have also been identified. These mutations increase production of the aggregation-prone A β_{42} relative to the more soluble A β_{40} . With regard to LOAD, one of the most influential associated genetic loci is ApoE, an apolipoprotein considered central to regulating A β production and clearance. Whether or not APP is cleaved first by α -secretase or BACE is a critical juncture in determining A β_{42} production. For this reason, understanding what determines this *in vivo* is almost certainly paramount to understanding the physiological and pathological roles of APP. Additionally, what regulates γ -secretase cleavage of CTF β to yield A β of various lengths on the amyloidogenic side of the APP processing pathway appears to be poorly understood. This is despite the difference of just two amino acids profoundly affecting A β aggregation ability. If indeed A β_{42} causes AD, then obtaining this understanding is a pressing matter.

Given that BACE commits APP down the amyloidogenic processing pathway, targeting BACE activity has been presented as a reasonable proposition for reducing A β production (Prati et al., 2018). Though some have argued that the experimental basis for this proposition is scant (Imbimbo and Watling, 2019), preclinical studies show inhibiting BACE1 activity lowers brain A β levels and rescues cognitive deficits in AD model mice. This has motivated at least 17 clinical trials taking this approach to treat early-stage AD. Unfortunately, all of these trials have failed for reasons of toxicity and in some cases *worsening* of cognitive function. This is despite often achieving major reductions in A β in cerebrospinal fluid (Imbimbo and Watling, 2019). Why these trials failed has been discussed extensively but possible reasons include poor selectivity of experimental compounds between BACE1 and BACE2, inadequacies in preclinical experimental models, or simply a lack of credibility in the amyloid cascade hypothesis. A further concern is that APP is far from being the only substrate of BACE1 so its inhibition may produce many off-target effects. Other BACE1 substrates include A β precursor like protein 1 (APLP1), A β precursor like protein 2 (APLP2), contactin-2, jagged 1, ADAM10 and sortilin related receptor 1 (SORL1). Assumedly, inhibiting BACE1 activity would also reduce production of A β_{40} , which like A β_{42} may have important physiological roles in cognition and beyond. Additionally, inhibiting BACE1 activity may direct APP processing further down the line of non-amyloidogenic processing. This may be beneficial insofar it reduces the production of amyloidogenic A β_{42} though the full outcome of increasing α -secretase cleavage of APP is unclear. Indeed, the physiological function of APP and its many proteolytic fragments is far from limited to just the effects of A β . As such APP likely constitutes a package of signaling molecules that likely operate throughout the body. Indeed, a whole field of research has sprung up around the physiological effects of APP and its derivatives showing effects ranging from cell adhesion, trophic functions, axon pruning, intracellular signaling to apoptosis to name a few (Brothers et al., 2018; Carrillo-Mora et al., 2014; Guo et al., 2012; Kent et al., 2020; Koudinov and Berezov, 2004; Ludewig and Korte, 2016; Muller et al., 2017; Muller and Zheng, 2012; Nalivaeva and Turner, 2013; Puzzo and Arancio, 2013; Puzzo et al., 2015a; van der Kant and Goldstein, 2015). For instance, AICD alone is implicated in neuronal migration, synaptic plasticity, cell death, DNA repair, nuclear signaling and neuromuscular synaptic deficits. To gain an idea of how complex and multifunctional just AICD alone is the reader is referred elsewhere (Bukhari et al., 2017).

APP was initially identified in 1987 in an endeavor to identify the origin of amyloid deposited in AD and Down's syndrome (Kang et al., 1987). APP belongs to a family of APP-like proteins that include two other APP-like proteins, APLP1 and APLP2 that are widely expressed in the nervous system. Though A β cannot be generated from these other proteins, there is sizable overlap in function though the functions of APLP1 and APLP2 are relatively unknown. APP knockout mice are viable and fertile and generally exhibit a mild phenotype. Nonetheless, they do display several abnormalities including alterations in cholesterol metabolism, defective LTP and learning deficits (see Guo et al., 2012). The apparent phenotype of APLP1 or APLP2 knockout mice is even milder than APP knockout mice, though arguably there has been less motivation to identify phenotypes. Notably they appear normal in learning tasks and show no obvious postnatal growth defects. In contrast, double knockout of both APP and APLP2, or APLP1 and APLP2, produces mice that die soon after birth suggesting redundancy among members of the APP family. Interestingly, APP/APLP1 double knockout mice are viable. On first presentation, these studies might suggest only a minor role for APP in the development and functioning of the nervous system. However, I contend that employing APP knockout mice to uncover the role of APP-derived peptides may require a question more appropriate to the physiological function of APP and maintaining mice in appropriate environments.

Naturally, much of the interest in A β_{42} has focused on potential toxic properties, which are now primarily attributed to oligomeric forms. The catalogue of cellular toxicities accredited to oA β_{42} is massive and will not be covered in detail here. Mitochondrial dysfunction, oxidative stress, synaptic dysfunction, membrane dysfunction, microglial activation, perturbations in Ca²⁺ homeostasis and endoplasmic reticulum stress are but a few (Carrillo-Mora et al., 2014; Chen et al., 2017; Ferreira and Klein, 2011; Fontana et al., 2020; Leong et al., 2020; Marttinen et al., 2018; Viola and Klein, 2015; Yankner and Lu, 2009). These toxicities reverberate through brain circuits and nuclei commonly implicated in AD including neocortical, hippocampal and cortical regions (Raskin et al., 2015) and specific nerve tracts such as basal cholinergic neurons and midbrain NE neurons. Multiple intracellular and extracellular cascades are impacted with some of the most predominantly studied including Wnt signaling, 5' adenosine monophosphate-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), sirtuin 1 (Sirt1), silent mating-type information regulator 2 homolog 1, peroxisome proliferator-activated receptor gamma co-activator 1- α (PGC-1 α), Notch signaling, MAPK signaling and ubiquitin mediated proteolysis (Crews and Masliah, 2010; Mizuno et al., 2012; Raskin et al., 2015). Indeed, this list far from credits the complexity of the pathways impacted in AD and as the recognized number of pathways grow there have been increasing attempts to integrate these pathways into a single schema. For a simplified overview, the reader is referred to the KEGG database (<https://www.genome.jp/kegg/pathway.html>) and AlzPathway (<http://alzpathway.org/AlzPathway.html>). Furthermore, these effects are unlikely to be a one-dimensional process but likely change spatiotemporally as the disease passes through various stages.

Given that aggregation of A β_{42} is central to its toxicity significant effort has been directed towards understanding the conditions under which aggregates form, disaggregate and are cleared (Lee et al., 2017a; Yerbury et al., 2016) as based on the amyloid cascade hypothesis targeting aggregation A β_{42} aggregation seems a viable approach to treating or preventing AD (Giorgetti et al., 2018; Zaman et al., 2019). Protein aggregation is influenced by many physical factors such as protein concentration, temperature, ionic environment and pH, and interactions with biomolecules such as gangliosides, serum proteins, apolipoproteins, complement component C1q, phospholipids and metal ions such as Cu²⁺ and Zn²⁺ (McLaurin et al., 2000; Wang et al., 2010c; Zaman et al., 2019). Given that A β is itself derived from a partial membrane spanning sequence of amino acids, an interesting line of enquiry has been in the

ability of A β to impact membrane conductances (Fabiani and Antollini, 2019; Tofoleanu and Buchete, 2012). Moreover, recent studies suggest membranes themselves promote self-assembly of A β aggregates at nM concentrations (Banerjee et al., 2017; Banerjee et al., 2020; Khondker et al., 2017). However, how these factors operate in vivo is largely unclear and arguably overlooked given the view that amyloids can take on important functional properties. To give just two more examples, complement C1q binds A β and regulates its aggregation. Complement C1q is a protein complex elemental to the body's innate immune system and evidence suggests it marks pTau-containing synapses for pruning (Dejanovic et al., 2018); a process that may serve important physiological processes (see section 21.1). Gangliosides are important elements of lipid raft membrane microdomains important to organizing membrane-bound molecules found in post-synaptic clusters into functional domains (Grassi et al., 2020; Hicks et al., 2012). A better understanding of protein aggregation and disaggregation, particularly in vivo and under biological conditions would not only pave the way for uncovering the physiological role of aggregating proteins but could also guide therapeutic development. With respect to this, over a dozen compounds with anti-aggregation properties are currently under study for treating AD (Giorgetti et al., 2018).

The list of known A β binding sites and interaction partners continues to grow (**Table 2**) (see Ferreira et al., 2015; Guo et al., 2020; Jarosz-Griffiths et al., 2016; Li et al., 2017b; Mroczko et al., 2018; Smith and Strittmatter, 2017; Xia et al., 2016). Determining if these binding partners are physiologically or pathologically important in vivo seems a daunting but important task. Even data regarding the binding kinetics for already known binding sites is patchy (Smith and Strittmatter, 2017). However, knowing these kinetics is critical to matching in vivo roles to the concentrations of A β found in biological compartments. Microdialysis studies in mice (Cirrito et al., 2003) and humans (Brody et al., 2008) suggest mA β_{42} is found in pM concentrations in interstitial fluid, and oA β_{42} in the very low pM range in mice (Takeda et al., 2013). To put this in context, neuropeptide Y, which is considered one of the most abundantly expressed neuropeptides in the brain is estimated to exist in very low nM concentrations in the mediobasal hypothalamus (Thompson et al., 1995).

5. A β , neuroplasticity and memory

5.1. Modulation of synaptic efficacy

Long-term changes in synaptic efficacy are the most favored model of memory storage in the brain (Abraham et al., 2019; Korte and Schmitz, 2016; Langille and Brown, 2018; Smolen et al., 2019). The principal mechanisms by which these occur are LTP, which strengthens synaptic efficacy, and LTD, which weakens synaptic efficacy. However, these are not the only means by which synaptic efficacy can change. Other processes such as depotentiation, which is considered distinct from LTD, can reverse established LTP (Wagner and Alger, 1996). It is important to note that LTP and LTD are biological constructs. It is easy to gain the impression that synaptic potentiation occurs in an almost binary fashion like transistor states in a digital computer - either potentiated or not. However, strengthening of synaptic efficacy occurs over a sliding scale producing a highly dynamic system whereby LTP, LTD and depotentiation achieve desired levels of potentiation.

The vast majority of studies focusing on changes in synaptic efficacy focus on potentiation or depotentiation as separate entities. Infrequently are more complex issues investigated such as if a factor that induces LTD reverses established LTP. For example, studies show that whether the two processes interact cooperatively or interfere depends on the time interval between when they are induced (Pavlovsky and Alarcon, 2012). This is not a trivial point as understanding how neuronal connectivity is

established, maintained, *adjusted* and *reversed* on a network level is extremely important. This is an issue approached in the study of homeostatic synaptic scaling (Chowdhury and Hell, 2018) and synaptic metaplasticity (Abraham, 2008), which emphasize that though LTP and LTD are opposites, the two processes balance and limit each other. That is, LTP can prevent synaptic strength becoming too weak, and, LTD can prevent LTP becoming too strong. This point too is important because one would be forgiven for thinking reading the AD-research literature that LTD is a purely negative event, acting to harmfully wipe out memories encoded in potentiated circuits. In fact, LTD may not only serve to protect plasticity and overexcitation, but may even be elemental to forming network level memory in the same way complex processing require a variety of logic gates or Boolean operators.

5.2. A β and neuroplasticity

Given the above, it is unsurprising that the cellular mechanisms of LTP and LTD share many commonalities. These include trafficking and phosphorylation of NMDARs and AMPARs and alterations in intracellular Ca²⁺ concentrations (Bliss and Cooke, 2011). Multiple approaches have studied the impact of A β ₄₂ on synaptic plasticity including administration of mA β ₄₂ or pre-aggregated oA β ₄₂ to in vitro preparations or wildtype rodents, and studying mice expressing human AD-related genes. However, it would be amiss to not emphasize that the validity of these models has come under increasing scrutiny (e.g. Foidl and Humpel, 2020; King, 2018; Krstic and Knuesel, 2013; Sasaguri et al., 2017; Zahs and Ashe, 2010) and comprehensive reviews of findings can be found elsewhere (see LaFerla and Green, 2012; Parihar and Brewer, 2010; Vyas et al., 2020). It suffices to say that the overriding narrative is that by forming oligomers, A β ₄₂ disrupts LTP (Li et al., 2011), promotes LTD (Li et al., 2009) and decreases dendritic spine density (Wu et al., 2010). To many, these findings substantiate the view that A β ₄₂ acts largely with sinister intentions. However, there is increasing recognition that A β ₄₂ and other APP-derivatives play important beneficial roles in modulating synaptic plasticity (Li et al., 2017b; Morley et al., 2019; Parihar and Brewer, 2010; Puzzo et al., 2012; Ricciarelli and Fedele, 2018; Venkitaramani et al., 2007) including metaplastic events such as STC and synaptic scaling (Galanis et al., 2020; Gilbert et al., 2016; Jang and Chung, 2016; Li et al., 2017a; Megill et al., 2015; Peineau et al., 2018). This is not to say that A β ₄₂ is always harmless (see section 21), indeed there is little doubt A β ₄₂ *can* be very toxic at certain concentrations and in certain forms. However, the questions are: in what form is A β ₄₂ toxic, at what concentration, does it serve a natural function, is it present in AD patients and does it drive AD?

Many different intracellular signaling pathways have been implicated in the effects of A β ₄₂ on synaptic plasticity including those involving NMDARs (particularly GLUN2B subunits), glycogen synthase kinase- β (GSK3 β), mTOR, insulin signaling, Ca²⁺ signaling, extracellular signal-regulated kinase 1/2 (ERK1/2) signaling and phosphoinositide 3-kinases/Akt (PI3K/Akt) signaling to name just a few (Guntupalli et al., 2016; Ma and Klann, 2012; Parihar and Brewer, 2010). Evidence is mounting that certain forms of A β are not only beneficial, underlying neurotrophic actions, neuroprotection and important memory processes (see Crdenas-Aguayo et al., 2014; Li et al., 2017b; Ludewig and Korte, 2016; Peineau et al., 2018; Puzzo, 2019; Puzzo and Arancio, 2013; Ricciarelli and Fedele, 2018). For example, though APP knockout does not produce a striking phenotype, APP knockout mice do exhibit LTP deficits (see Korte et al., 2012; Muller et al., 2017; Vyas et al., 2020), reduced spine density (Weyer et al., 2014) and memory impairments (Senechal et al., 2008). It is now apparent that APP KO mice exhibit several impaired phenotypes that could impact cognitive function (Korte et al., 2012; Muller et al., 2017; Vyas et al., 2020). Likewise, BACE1 knockout mice also exhibit impaired memory and synaptic plasticity (Laird et al., 2005), though several studies show improvements in memory (see Munro et al., 2016 for references). Anti-A β antibodies or siRNA targeting APP reduces LTP and impairs contextual fear memory and reference memory (Puzzo et al., 2011). Concerns over developmental compensations aside, studies

knocking out APP or factors involved in APP processing may be more capable of revealing physiological function than those adding to endogenous A β pools. Regardless, mA β_{42} administration in the mid picomolar (200 pM) *promotes* hippocampal LTP and enhances reference and contextual memory; an effect involving α_7 -nicotinic receptors (α_7 NicR) (Puzzo et al., 2008). Increasing extracellular A β levels boosts hippocampal activity coincident with enhancing synaptic release probability, an effect that weakens as firing rates increase (Abramov et al., 2009). Notably, neuronal activity stimulates increases in extracellular A β levels (Cirrito et al., 2005) and human studies show that areas of the brain with the highest metabolic activity are those that accumulate A β and degenerate (Buckner et al., 2005). Together with a range of other direct and circumstantial evidence (see Carrillo-Mora et al., 2014; Crdenas-Aguayo et al., 2014; Guo et al., 2012; Kent et al., 2020; Koudinov and Berezov, 2004; Morley and Farr, 2012; Muller et al., 2017; Muller and Zheng, 2012; Parihar and Brewer, 2010; Peineau et al., 2018; Puzzo and Arancio, 2013; Puzzo et al., 2015a; Ricciarelli and Fedele, 2018) there is strong reason to believe that A β at physiological concentrations promotes synaptic strengthening and helps maintain it in a homeostatic range.

As yet, pro-plasticity properties of A β_{42} have been identified for low concentrations of mA β_{42} . The effects of low concentrations of oA β_{42} are less understood though it is clear is that high oA β_{42} concentrations impair synaptic plasticity (Palop and Mucke, 2010; Selkoe, 2008; Tu et al., 2014). This draws attention to at least two important factors impacting interpretation of this type of data: concentration and oligomerization state. Predicting how concentrations achieved by exogenous administration or overexpression of APP relate to endogenous concentrations, especially at the site of action is challenging. Complicating the issue further, there have been many different methods of oligomer preparation over the years, which almost certainly impact their synaptic effects (Viola and Klein, 2015). Even the potency of AD brain extracts varies substantially (Li et al., 2018). Nonetheless, it is increasingly apparent mA β_{42} acts in a hormetic fashion (Carrillo-Mora et al., 2014; Lanni et al., 2019; Lazarevic et al., 2017; Morley and Farr, 2012; Morley et al., 2019; Puzzo et al., 2012; Ricciarelli and Fedele, 2018): low concentrations promote LTP and memory formation, acting at least partially through α_7 NicRs. High concentrations are detrimental to LTP and promote LTD. These effects correspond well with binding studies showing mA β_{42} affinity for α_7 NicRs in the pM range (Palop and Mucke, 2010; Wang et al., 2000b); a range corresponding to that found in interstitial fluid (Cirrito et al., 2003). This leads one to consider how one's choice of words influences one's understanding of function. Viewed from one angle, the effects of higher concentrations of A β_{42} on LTP may appear "detrimental", but viewed from another, they may be viewed as protective against over-excitation. Indeed, as A β_{42} is secreted during neuronal activity, switching from initial pro-LTP to pro-LTD actions as concentrations build, some have speculated that endogenous A β_{42} constitutes a negative feedback mechanism that maintains synaptic plasticity in an appropriate dynamic range (Kamenetz et al., 2003; Palop and Mucke, 2010; Parihar and Brewer, 2010; Stargardt et al., 2015; Venkitaramani et al., 2007). In support of this, LTP is enhanced at the expense of LTD in young APP^{swe};PS1 Δ E9 transgenic mice but reverses to LTD strengthening and LTP reducing with age (Megill et al., 2015). Low dose NMDA administration increases synaptic A β levels while raising synaptic transmission. On the other hand, high doses of NMDA turn APP processing away from A β production despite elevated synaptic activity (Verges et al., 2011). This suggests an endogenous mechanism designed to limit over-production of A β_{42} .

As concentrations of mA β_{42} increase, a beneficial neuroprotective action via antagonism of α_7 NicRs develops into a pathological action as concentrations rise and oligomers form (Sadigh-Eteghad et al., 2014). How A β_{42} impacts LTP via α_7 NicRs is not fully resolved. Both agonistic and antagonistic effects of A β_{42} have been reported though the dominant view is that pM concentrations of A β_{42} activate α_7 NicRs whereas high concentrations are inhibitory (see Buckingham et al., 2009; Lasala et al., 2019 for

references). A β_{42} application at high concentrations (1 μ M) induces endocytosis of NMDARs and depression of NMDA-evoked currents, recruiting calcineurin (PP2B) and the plasticity-modulating protein striatal-enriched tyrosine phosphatase (STEP, Snyder et al., 2005). The involvement of calcineurin in this process is particularly salient as calcineurin has a venerable association with constraining LTP and inducing LTD and depotentiation (Baumgartel and Mansuy, 2012) and forgetting (Sachser et al., 2016). Driven to its extreme, as may occur during overaccumulation of A β_{42} calcineurin may drive loss of synapses and memory (see Spires-Jones and Hyman, 2014). STEP itself is important in regulating glutamate receptor phosphorylation and internalization, in addition to phosphorylating protein tyrosine kinase 2 β (Pyk2) and being dysregulated in AD mouse models (Kamceva et al., 2016; Lombroso et al., 2016). Together, data such as these lend support to the notion that before becoming neurotoxic, A β_{42} mediates important beneficial actions in determining synaptic efficacy.

6. Control of APP processing

Given the wide range of APP derivatives and possible functions, understanding in vivo control of APP processing in vivo is central to understanding APP and A β function (Chen et al., 2017; Chow et al., 2010; Nalivaeva and Turner, 2013; Zhang and Song, 2013; Zhang et al., 2011). Some important questions include: What controls commitment to non-amyloidogenic versus amyloidogenic processing? What determines cleavage of A β peptides by γ -secretase into different length isoforms and the various N- and C-terminal truncated A β forms found in vivo and what are the functions of these variants (Wirths and Zampar, 2019)? To what degree do various A β isoforms interact with each other either directly or indirectly and what are the outcomes? For example, recent studies suggest shorter A β peptides protect against toxic effects of A β_{42} (Moore et al., 2018). Given that secretases have many substrates other than APP, what if anything, confers selectivity over APP processing?

Questions such as these have led to speculation that relative concentrations of A β isoforms, especially the ratio of A β_{42} to A β_{40} , may be just as important as the concentration of any given isoform. For instance, plasma A β_{42} :A β_{40} ratio predicts cortical amyloid burden (Fandos et al., 2017) and may have stronger diagnostic value than concentrations of A β_{42} alone (see Lehmann et al., 2018). Mutations in APP and PSEN1 believed to drive FAD not only increase A β generally but also shift the ratio towards proportionately higher A β_{42} levels. This change in ratio may impact aggregation of A β_{42} (Jan et al., 2008) as well as lessen neuroprotective effects of A β_{40} . Studies suggest higher A β_{42} :A β_{40} ratios favor production of further higher ratios by a reciprocal modulation of PSEN1 (Zoltowska et al., 2016), an effect that may itself involve the presynaptic protein synaptotagmin (Zoltowska et al., 2017). This suggests a mechanism by which aggregation of A β_{42} promotes its own aggregation. On the other hand, activation of M1/M3 muscarinic receptors directs APP processing toward the non-amyloidogenic secretory pathway by activating α -secretase activity (see Rossner et al., 1998). mGluR1 is also capable of turning APP processing towards the non-amyloidogenic pathway (Lee et al., 1995). Several other G-protein coupled receptors are implicated in regulating α -secretase activity, including serotonin, adrenergic, corticotropin releasing hormone, mGluRs and ADCYAP receptor type I receptors (Cheng et al., 2014; Thathiah and De Strooper, 2011). Particularly interesting is that many of these receptors transduce the actions of neuromodulators released from the isodendritic core of the brain – an observation that may enlighten how such broadcast neuromodulators modulate learning and long-term retention of memory (see sections 15, 18).

Known modulators of BACE1 activity are numerous, including possible roles for eukaryotic initiation factor-2 α (eIF2 α) kinase, nogo proteins, SORL1, nuclear factor NF- κ B, heparan sulfate, sphingosine-1-

phosphate, copper chaperone for superoxide dismutase, brain protein I3, F2R-like thrombin or trypsin receptor 3, δ -opioid receptors, mGluRs, NMDARs, prion protein and adenosine A2a receptor (Adora2A) (Cheng et al., 2014; Cole and Vassar, 2007; Parkin et al., 2007; Takasugi et al., 2011; Thathiah and De Strooper, 2011). For instance, through an interaction with APP, nogo decreases cell surface APP expression and promotes processing by BACE1 (Zhou et al., 2011). Among the many putative and confirmed substrates of BACE1 (Yan and Vassar, 2014) is SORL1, which regulates intracellular transport and processing of APP. Polymorphisms in SORL1 are associated with cognition and are among the genes more highly associated with LOAD. Indirect evidence suggests that SORL1, BACE1, and γ -secretase form a complex to cleave APP, which is interesting as polymorphisms or mutations in all four of these proteins have been linked to LOAD (Barthelson et al., 2020). SORL1 exhibits molecular interactions that could place it centrally in controlling synaptic plasticity. Activation of α_2 -adrenergic receptors promotes A β production by disrupting interaction of SORL1 with APP (Chen et al., 2014). SORL1 also sorts the BDNF receptor neurotrophic receptor tyrosine kinase 2 (TrkB) and increasing SORL1 by BDNF administration reduces A β levels in mice (Rohe et al., 2009). γ -secretase activity is also under the control of several G-protein coupled receptors including G protein-coupled receptor 3, C-X-C motif chemokine receptor 2 (Thathiah and De Strooper, 2011), dopamine receptor D2 (Lu et al., 2017) and β_2 -adrenergic receptors (Thathiah et al., 2013). Other regulators may include group II mGluRs and leptin receptors (Cheng et al., 2014). These findings, which are unlikely to be exhaustive, highlight the complexity of APP processing.

7. PRPC as a receptor mediating A β effects on memory persistence

Well over 40 different molecules have been reported to bind A β , many of which were discovered in endeavors to identify loci of synaptotoxic actions (Chen et al., 2017; Jarosz-Griffiths et al., 2016; Lai and McLaurin, 2010; Mroczko et al., 2018; Smith and Strittmatter, 2017). Distinguishing which are of physiological relevance, pathological relevance or both is likely to be a lengthy affair. It would be premature to assume that because an A β binding partner (sometimes called A β receptors) has no known direct relationship to mnemonic processes it is not worthy of investigation. Nonetheless, several obvious candidates stand out. These include AMPRs, NMDARs, calmodulin, mGluRs, muscarinic receptors, adrenergic receptors, nicotinic receptors and PRPC. To be seriously considered, A β binding partners should fit at least a basic set of criteria including reasonable specificity for A β binding, binding of A β at concentrations of A β existing at the predicted locus of action (e.g. within the synaptic cleft, interstitial space etc.) and of course, elicit some physiological or pathological response.

Among the known binding partners of A β , PRPC is particularly significant as it fits these criteria well. Binding of A β to PRPC was discovered by the Strittmatter and colleagues in pursuit of sites at which oA β_{42} may exert pathological actions (Brody and Strittmatter, 2018). Using a non-biased screen of oA β_{42} binding in an adult mouse brain library of 225,000 cDNAs expressed in Cos-7 cells, Strittmatter *et al* singled out 15 strong candidate binding partners. PRPC emerged as binding oA β_{42} with high affinity and showing the largest reduction of oA β_{42} binding when removed from hippocampal neurons (Smith et al., 2019). Recent studies show blocking oA β_{42} binding to PRPC restores synapse loss and memory deficits in AD model mice (Gunther et al., 2019). Of particular interest is that PRPC binds only oA β_{42} and with low nanomolar affinity, showing little affinity for the monomeric form; a finding recently corroborated by in vitro studies, though interestingly these studies suggest that PRPC does not mediate the neurotoxic effects of oA β_{42} (Mengel et al., 2019). oA β_{42} bind PRPC in a concentration range concordant with that found in AD sufferers and transgenic mouse models, though whether or not oA β_{42} is found bound to PRPC in actual AD brains is currently unclear. oA β_{42} derived from patients binds dendrites of cultured mouse hippocampal neurons in a highly specific manner (Gong et al., 2003) and several studies show

binding of AD patient-derived (but not healthy patient-derived) $\text{oA}\beta_{42}$ oligomers to PRPC (Dohler et al., 2014). However, the degree to which binding may relate to the higher $\text{A}\beta_{42}$ load found in AD brains is unclear and currently does not exclude the possibility of $\text{oA}\beta_{42}$ binding in healthy brains. Though its relevance, if any at all, is unclear, PRPC display a peculiar likeness to APP inasmuch that PRPC also undergoes α , β and possibly γ -cleavage and forms a protein with notorious aggregating ability (Altmeppen et al., 2012). Moreover, there appears to be a direct interaction as PRPC suppresses $\text{A}\beta_{42}$ production (Parkin et al., 2007).

Uncovering the physiological purpose of PRPC has been of intense interest ever since its discovery. PRPC is highly conserved in mammals and widely distributed in the brain, especially in areas associated with ongoing plasticity (Sales et al., 1998). PRPC is expressed in neurons and glia, mainly on the cell surface as a glycosylphosphatidylinositol-anchored protein localized to lipid rafts. Though PRPC was, and understandably so, initially viewed as a *bête noire*, it is becoming clear that it serves many important physiological functions by interacting with extracellular and intracellular partners (**Table 3**) (Aguzzi et al., 2008; Castle and Gill, 2017; Didonna, 2013; Gavin et al., 2020; Linden, 2017; Miranzadeh Mahabadi and Taghibiglou, 2020; Peggion et al., 2017; Puig et al., 2020; Schneider et al., 2011; Sorgato et al., 2009; Watts et al., 2018; Wulf et al., 2017). Importantly, unlike APP, PRPC does not possess an intracytoplasmic tail and appears to act as a co-receptor serving as a conduit for various extracellular and membrane molecules. As such, PRPC appears to function as a multipurpose binding point for mediating signaling by recruiting other signaling molecules. By this means PRPC controls processes including cell adhesion, proliferation, differentiation, neurite outgrowth, neuronal excitability and calcium homeostasis. A major function of PRPC may be to mediate $\text{A}\beta$ control of cell surface proteins such as neurotransmitter receptors and adhesion molecules (Linden, 2017; Sorgato et al., 2009; Wulf et al., 2017). $\text{A}\beta$ may not be the only aggregating protein PRPC binds as though evidence is inconsistent, studies suggest binding also to aggregates of α -syn and tau (Corbett et al., 2020; De Cecco et al., 2020; La Vitola et al., 2019; Urrea et al., 2017).

Natural mutations in PRPC are very rare where they cause familial Creutzfeldt-Jakob disease (CJD), Gerstmann–Sträussler–Scheinker syndrome, and fatal insomnia (Bernardi and Bruni, 2019). Genome-wide association studies identify very few polymorphisms in the PRNP gene and those that are known associate with CJD or unclear dementia phenotypes including AD-like phenotypes (see Bagyinszky et al., 2018). The familial form of CJD develops in the early 50s and is similar enough to LOAD in symptomatology that differential diagnosis is difficult (Chitravas et al., 2011; Tschampa et al., 2001). This leads one to speculate that PRNP mutations and polymorphisms may be more common in AD than currently recognized. However, given that prion diseases are so rare, genetic variation in PRPN does not appear to be a major cause of AD though this does not negate PRPC as being permissive to disease progression.

To date, the vast majority of studies of the involvement of PRPC in mediating $\text{A}\beta$ effects have focused on $\text{oA}\beta$ -induced toxicity. For the sake of brevity, these studies will be not reviewed here as they have been covered in several recent reviews (see Nygaard and Strittmatter, 2009; Zhang et al., 2019b). It is important to consider that for many interactions between PRPC, $\text{A}\beta$ and other molecules it is currently unclear if they lie on physiological-pathological spectrum and if so, where. This renders all studies potentially important to understanding the physiological function of $\text{A}\beta$ -PRPC interaction. Though the weight of evidence (see Brody and Strittmatter, 2018; Li et al., 2017b; Nasica-Labouze et al., 2015) favors a role for PRPC in mediating $\text{A}\beta_{42}$ effects on synaptic plasticity (Gimbel et al., 2010) conflicting findings exist (e.g. Balducci et al., 2010; Calella et al., 2010; Cisse et al., 2011; Kessels et al., 2010). Some of these disparities may reflect perennial issues in modeling AD in experimental animals including limitations in the ability of current techniques to characterize $\text{A}\beta$ oligomers (see Nasica-Labouze et al.,

2015) or the questionable validity of some genetic mouse models (Drummond and Wisniewski, 2017; Gotz et al., 2018; King, 2018; Puzzo et al., 2015b; Sasaguri et al., 2017; Zahs and Ashe, 2010).

As PRPC has no intracellular tail it alone is not equipped to transduce signals to the intracellular compartment. Rather, as introduced above, PRPC acts as a cell surface scaffold forming complexes with other membrane proteins mediating effects ranging from neuroprotection to neurotoxicity (Beland and Roucou, 2012; Didonna, 2013; Linden, 2017; Linden et al., 2012). Over 50 proteins are reported to interact with PRPC including clusterin, 37/67 kDa laminin receptor (LRP/LR), laminin, neuronal cell adhesion molecule 1 (NCAM1), stress induced phosphoprotein 1 (STI1), mGluR1, mGluR5, α -NicRs, NMDARs and potassium channels (via dipeptidyl peptidase like 6). Several of these have clear links to synaptic plasticity (**Table 3**) the first of which that will be discussed is mGluR5.

8. The PRPC-mGluR5 complex as a mediator of A β write-protection

mGluR5 was identified by the Strittmatter group (Um et al., 2013) as a coreceptor of PRPC from an unbiased screen of post-synaptic density (PSD)-enriched transmembrane receptors via which oA β ₄₂ induces Fyn (Src-like kinase) phosphorylation (see Brody and Strittmatter, 2018). There has been a long-standing interest in the role of glutamatergic transmission in AD (see Danysz and Parsons, 2012 for a review of NMDAR involvement particularly) fueled partially by the beneficial though mild effects of the NMDA receptor antagonist memantine in treating AD. Over the years there has been considerable interest specifically in mGluR5 in AD and other neurological disorders, particularly fragile X syndrome and autism (Benarroch, 2018; Crupi et al., 2019; Kumar et al., 2015). This relates particularly to the central function of mGluR5 in experience-dependent plasticity including late-phase LTP, LTD, metaplasticity, synapse elimination/refinement, cognitive aging, extinction learning and long-term neuroplasticity (Bhattacharyya, 2016; Mukherjee and Manahan-Vaughan, 2013; Simonyi et al., 2005; Watterson and Olive, 2014).

mGluR5s are widely expressed throughout the forebrain with highest levels found in the dentate gyrus, showing in mouse brain a remarkably similar expression pattern as PRPC and GRIN2B (**Fig. 1**). mGluR5s are typically localized to the periphery of the post-synaptic area where via activation of phospholipase-C and generation of diacylglycerol and inositol 1,4,5-trisphosphate their activation releases Ca²⁺ from intracellular stores. This activates PKC, engaging a range of downstream effectors. mGluR5s play a multi-functional role in plasticity, having functions in LTP (Mukherjee and Manahan-Vaughan, 2013), LTD and synaptic depotentiation (Jones, 2017; Luscher and Huber, 2010) and of particular relevance here, mGluR5 knockdown rescues some of the pathologies in APPswe/PS1 Δ E9 mice (Hamilton et al., 2014). Notably, group 1 mGluRs (of which mGluR5 is one) have been suggested to constitute a “molecular switch” that is toggled by high frequency synaptic input during LTP induction thereafter holding the synapse in a potentiated state that can be switched back by low frequency stimulation (Bortolotto et al., 1994).

There is a growing recognition that mGluR5 interacts with PRPC to form a functional complex transducing the effects of various PRPC ligands, limited not only to A β but also including α -syn (Beraldo et al., 2016; Ferreira et al., 2017; Scialo and Legname, 2020). Interestingly, some of these interaction partners such as ganglioside GM1, laminin and α B-crystalline can influence A β aggregation (Bronfman et al., 1998; Ikeda et al., 2011; Raman et al., 2005). Given evidence that PRPC mediates at least some of the neurotoxic effects of oA β ₄₂ on neuroplasticity there is reasonable grounds to believe that an oA β ₄₂-PRPC-mGluR5 complex plays a physiological role in modulating synaptic plasticity. This process is

blockable by allosteric modulators of mGluR5 which when administered to AD model mice, abrogate decreased synaptic density and memory deficits (Haas et al., 2014; Hamilton et al., 2016; Um et al., 2013) and restore LTP impairments induced by oA β_{42} (Rammes et al., 2011). Studies to date have generally interpreted these effects in the light of neurotoxicity (see Haas et al., 2016; Jarosz-Griffiths et al., 2016; Lima-Filho and Oliveira, 2018; Miranzadeh Mahabadi and Taghibiglou, 2020; Nygaard and Strittmatter, 2009; Peggion et al., 2017; Purro et al., 2018; Watts et al., 2018; Zhang et al., 2019b). However, under non-diseased physiological conditions where endogenous A β_{42} levels are lower, the PRPC-mGluR5 complex may be a substrate through which A β_{42} and other molecules act to maintain, limit and protect established neuroplasticity from modification by continued excitatory synaptic input. Such a role for mGluR5 would be in keeping with the suggested role of group 1 mGluRs as molecular switches mentioned above.

As mA β_{42} levels rise with continued synaptic input, mA β_{42} and/or oA β_{42} may bind to PRPC and as an oA β_{42} -PRPC-mGluR5 complex promote synaptic depotentiation thus preventing overexcitation to ensure potentiated states remain in intended bounds. Though the majority of studies have focused on oA β_{42} binding to PRPC, recent studies by Abd-Elrahman and colleagues show direct binding of oA β_{42} to mGluR5, which itself is PRPC-dependent. Remarkably this binding is absent in female (but not male) mice and human tissue. Moreover, mGluR5 inhibition using CTEP does not rescue memory deficits maze in female APPswe/PS1 Δ E9 mice (Abd-Elrahman et al., 2020a). Generally, the binding of oA β_{42} to PRPC is portrayed as the initiating factor in forming the complete oA β_{42} -PRPC-mGluR5 complex (Brody and Strittmatter, 2018; Nygaard and Strittmatter, 2009; Peters et al., 2015; Smith and Strittmatter, 2017). Notably, the studies of Strittmatter's laboratory found no direct binding of oA β_{42} to mGluR5 (Um et al., 2013) or the necessity of mGluR5 expression (Brody and Strittmatter, 2018). In contrast, studies by Renner and colleagues (Renner et al., 2010) find oA β_{42} binding to neuronal surfaces severely limits the lateral diffusion of mGluR5 and is markedly reduced in cultures from mGluR5 knockout mice. Though their studies made no direct assessment of oA β_{42} to mGluR5, their results strongly implicate such a possibility, though whether or not this depends on other proteins was not investigated.

Together, these observations question the sequence of events in which oA β_{42} -PRPC-mGluR5 complexes are formed. As Renner and colleagues suggest, oA β_{42} may act as an extracellular scaffold bringing together PRPC and mGluR5 that ultimately acts to limit lateral diffusion of mGluR5s (Renner et al., 2010), perhaps with the deliberate intention of fixing them in place to preclude changes in plasticity. Although the study of Abd-Elrahman and colleagues was not designed to speak directly to the physiological role of PRPC-mGluR5 complexes under non-pathological conditions, it emphasizes the possibility of sex differences and along with related studies in the same model (Abd-Elrahman et al., 2020b), that roles of mGluR5 may change as AD progresses. Relatedly, even corrected for age, female sex is a negative risk factor for developing AD. Though this observation generally runs counter to PRPC-mGluR5 interactions as possibly endowing greater risk in women, it again underlines the importance of including sex as a factor in preclinical as well as clinical and epidemiological studies.

The intracellular pathways through which the mGluR5-PRPC complex promotes dampening of post-synaptic activity have been at least partially elucidated (Brody and Strittmatter, 2018; Hamilton et al., 2015). Again, it is important to re-iterate that studies to date have usually focused on neurotoxic effects using A β_{42} doses reflective of concentration ranges found in AD patients and mouse models. Using quantum dot-labeled oligomers and synaptic proteins, oA β_{42} has been shown to increase mGluR5 accumulation and reduce mGluR5 lateral diffusion, promoting clustering together (Renner et al., 2010). Formation and activation of the complex sets in motion a downstream response in effector proteins, some of which are classically involved in modulating synaptic efficacy. oA β_{42} binding to PRPC activates

FYN by phosphorylation, presumably via formation of the mGluR5-PRPC complex, giving way to several outcomes (**Fig. 2**). Firstly, Fyn activation phosphorylates NR2B subunits causing an initial increase but subsequent longer-term loss of NR2B from the cell surface (Um et al., 2012). NR2B is of particular interest as (1) it shows an expression pattern highly reminiscent of mGluR5 and PRNP (**Fig. 1**), (2) it is implicated in long-term plasticity and found in retrograde amnesia gene sets, and (3) overexpressing NR2B enhances memory (see Lee, 2014; Plattner et al., 2014).

Fyn activation leads to activation of eEF2 via activation of eEF2 kinase. eEF2 has many important roles in synaptic plasticity and learning (Taha et al., 2013) by generally suppressing translation of mRNAs but specifically increasing translation of several dendritic mRNAs involved in synaptic plasticity including calcium/calmodulin-dependent protein kinase II (CamKII), BDNF, microtubule-associated protein MAP1B and Arc (Heise et al., 2014). Many of these proteins belong to the fairly exclusive group of putative PRPs (**Table 1**). Arc for example is an important hub in controlling synaptic plasticity and refining synapses and its involvement in plastic changes associated with AD is becoming increasingly recognized (Kerrigan and Randall, 2013; Korb and Finkbeiner, 2011; Leung et al., 2019; Wilkerson et al., 2018). Arc also impacts spine reorganization by modulating the actin cytoskeleton to promote LTP or promoting LTD through AMPAR endocytosis. Arc also regulates APP and Notch1 processing via γ -secretase (Nikolaienko et al., 2018). mGluR-induced activation of eEF2 promotes spine stability via control of dendritic BDNF translation (Verpelli et al., 2010). **Figure 2** depicts a simplified scheme of some putative cellular pathways mediating A β ₄₂ effects on neuroplasticity and tau phosphorylation and aggregation.

Fyn activation also phosphorylates and activates Pyk2, leading to increased tau phosphorylation (**Fig. 2**) (Li and Gotz, 2018). Pyk2 is a non-receptor tyrosine kinase expressed particularly in hippocampal and cortical regions encoded by the Pyk2-encoding LOAD-risk gene PTK2B that regulates induction of LTP and LTD (Bartos et al., 2010; Hsin et al., 2010; Huang et al., 2001). oA β impairs the interaction between mGluR5 and Pyk2 by trapping PrPC-mGluR5 complexes in a glutamate-insensitive pathological state (Haas and Strittmatter, 2016). Knockdown of Pyk2 from mice suppresses induction of LTD specifically, with no effect on LTP (Hsin et al., 2010). Note however that other Pyk2 KO mice studies suggest Pyk2 is necessary for normal induction of LTP (Giralt et al., 2017). Remarkably, Pyk2 KO mice are protected from oA β ₄₂ suppression of synaptic plasticity and crossing Pyk2 KO mice with AD model mice rescues synaptic loss and learning/memory deficits without influencing oA β accumulation suggesting Pyk2 transduces a neurotoxic effect of oA β downstream of oA β accumulation (Salazar et al., 2019). Pyk2 potentially interacts with several AD-relevant intracellular targets including tau directly (Li and Gotz, 2018) and GSK3 β (Hartigan et al., 2001); a major kinase involved in tau phosphorylation, and growth factor receptor bound protein 2 (GRB2, Blaukat et al., 1999), an adaptor protein involved in regulating cytoskeletal dynamics (Lim and Halpain, 2000). GRB2 is found overexpressed in AD model mice and human AD-sufferers, which might reflect a compensatory attempt to maintain cytoskeletal stability as the disease progresses (see Majumder et al., 2017 for references). Phosphorylation of tau prevents interaction of tau with GRB2 (Reynolds et al., 2008) and variants in GRB2 predict the prognosis of disease progression in AD patients (Wang et al., 2020). Additionally, Pyk2 shows a remarkably similar pattern of brain expression (virtually confined to the forebrain) with Polo Like Kinase 2 (PLK2) – a serine/threonine protein kinase that regulates amyloidogenic processing of APP (Lee et al., 2019; Lee et al., 2017b) and implicated in homeostatic scaling (see Turrigiano, 2008).

oA β -PRPC toxically phosphorylates Fyn and tau (Larson et al., 2012; Um et al., 2012). Fyn has two-way relationship with tau (**Fig. 2**). Fyn phosphorylates tau (see Lee et al., 2004) and recent evidence suggests Fyn regulates the aggregation of tau (Briner et al., 2020). Tau on the hand is required for A β -induced localization of Fyn to the postsynaptic compartment (Ittner et al., 2010). Tau is normally an axonally-

located protein but NMDA activation or application of $\alpha\text{A}\beta_{42}$ induces phosphorylation of tau and its localization to the somatodendritic compartment (see Castro-Alvarez et al., 2014; Zempel et al., 2010). Interestingly, whereas NMDA receptor-dependent tau phosphorylation produced by chemically-induced LTD is reversible, this does not appear to be the case for tau phosphorylation induced by $\text{A}\beta_{42}$ (Mondragon-Rodriguez et al., 2012). pTau interacts with the PSD95-Fyn-NMDAR complex possibly leading to modulation of post-synaptic activity (Mondragon-Rodriguez et al., 2012). Though existence of tau in the somatodendritic compartment is generally viewed as “missorted” (see section 16.3), tau in dendrites may serve important physiological functions (Ittner and Ittner, 2018), (see Sotiropoulos et al., 2017). Synaptic activity and induction of LTP translocates tau into the PSD where it may regulate synaptic plasticity (Frandemiche et al., 2014) (see Regan et al., 2017). Notably, induction of LTD (but not LTP) critically depends on the presence of tau (Kimura et al., 2014b) suggesting dendritic tau may act to prevent overactivation of postsynaptic cells.

Recent studies suggest Fyn may also play roles in trafficking (Poulsen et al., 2017) and processing of APP (see Hartmann and Prinetti, 2011). Fyn promotes accumulation of phosphorylated APP in lipid rafts (Minami et al., 2011) and overexpression of Fyn directs its processing down the amyloidogenic pathway (Iannuzzi et al., 2020). Activation of NMDARs reduces excitatory synapses by MEF2 transcription factors likely acting through calcineurin (Flavell et al., 2006). Whether or not this effect is impacted by the PRPC-mGluR5 complex has not been directly tested but may be a worthy line of investigation as MEF2 plays an important role in activity-dependent synaptic weakening and pruning, including an action mediated by translation of Arc (Wilkerson et al., 2014). MEF2-triggered synapse elimination also depends on fragile X mental retardation protein (FMRP) (Pfeiffer et al., 2010), a protein implicated in homeostatic plasticity and synaptic remodeling via actin (Soden and Chen, 2010) (see Michaelsen-Preusse et al., 2018). Activation of Group 1 mGluRs modulates the interaction of FMRP with specific mRNAs including those mediating translation of APP in response to mGluR5 activation (Westmark and Malter, 2007).

The known involvement of many elements of this signaling cascade in neuroplasticity is striking. As mentioned above, calcineurin is a central node in intracellular networks governing LTD and is implicated in forgetting, synaptic scaling and constraining synaptic activity (Baumgartel and Mansuy, 2012; Kim and Ziff, 2014; Mansuy, 2003; Sachser et al., 2016). Polymorphisms in MEF2C are associated with LOAD (Lambert et al., 2013), intelligence (Hill et al., 2019b) and educational attainment (Lee et al., 2018a). Loss of FMRP function in fragile X mental retardation is accompanied by learning difficulties and age-dependent progressive deficits in working memory. FMRP has also been implicated in homeostatic scaling (Bulow et al., 2019; Lee et al., 2018b; Soden and Chen, 2010). Bear and colleagues theorized that exaggerated mGluR5-controlled LTD in response to loss of FMRP function underlies various psychiatric symptoms of Fragile X including memory deficits (Bear et al., 2004). Similar to the ability of inhibiting mGluR5 activity to reverse $\alpha\text{A}\beta$ -induced memory deficits, several aberrant phenotypes of fragile X model mice are reversible by the same means (see Erickson et al., 2017; Santos et al., 2014). mGluR5, FMRP and APP processing are interconnected (Westmark, 2019): mGluR5 increases APP translation by releasing FMRP repression of APP mRNA (Westmark and Malter, 2007). Activation of mGluR5 also increases Arc (Wilkerson et al., 2018), which may promote co-localization of APP and PSEN1 in endocytic vesicles leading to increased $\text{A}\beta$ production (Wu et al., 2011).

There has also been an increasing realization that $\text{A}\beta$ may impact presynaptic function as well as post-synaptic function, largely acting to inhibit presynaptic release (Gulisano et al., 2019; He et al., 2019; Moreno et al., 2009; Russell et al., 2012; Yu et al., 2018). This occurs through mechanisms including binding of APP fragments to presynaptic sites and modulation of presynaptic release machinery possibly working in concert with tau (Barthet and Mulle, 2020; Fagiani et al., 2019; Nimrich and Ebert, 2009;

Zhou et al., 2017). Recent studies show $\alpha\text{A}\beta_{42}$ decreases the release probability of presynaptic transmitters via mGluR5 (He et al., 2019). Thus, $\text{A}\beta$ may act on both sides of the synapse to limit over-excitation of post-synaptic neurons, placing it in a position to modulate the “synaptic homeostasis” proposed by Tononi and Cirelli as critical to memory formation (Tononi and Cirelli, 2014).

8.1. Other potential mechanisms mediating $\text{A}\beta$ effects on memory

The ability of PRPC to mediate $\text{A}\beta$ effects on synaptic transmission and plasticity are not limited to interactions with mGluR5. Potentially important exchanges of PRPC with elements occur on both sides of the synapse including interactions with integrins, neuronal nitric oxide synthase, α_2 -adrenergic receptors, voltage gated potassium channels, voltage gated Ca^{2+} channels, glutamate receptor subunits and mGluR1 (**Table 2**) (see Steinert, 2015). A particularly strong line of evidence is in the interaction of $\text{A}\beta$ with elements of cholinergic transmission either via PRPC or by direct binding to related molecules. Given the early degeneration of Ach fibers in AD, the established role of Ach in encoding memories (Haam and Yakel, 2017; Hasselmo, 2006; Teles-Grilo Ruivo and Mellor, 2013) and that boosting Ach transmission benefits cognitive deficits in AD, there has been long standing interest in Ach transmission in AD (Buckingham et al., 2009; Contestabile, 2011; Ferreira-Vieira et al., 2016; Francis et al., 1999; Hoskin et al., 2019; Inestrosa et al., 2005; Lombardo and Maskos, 2015; Oz et al., 2013; Parri et al., 2011; Schliebs, 2005; Shimohama and Kawamata, 2018; Yan and Feng, 2004). PRPC colocalizes with nicotinic receptor β_4 subunits (Petrakis et al., 2008) and forms a functional complex with $\alpha_7\text{NicR}$ subunits that promotes increases in intracellular Ca^{2+} (Beraldo et al., 2010). PRPC also regulates activation of $\alpha_7\text{NicR}$ where it plays a neuroprotective role (Jeong and Park, 2015). Picomolar concentrations of $\text{A}\beta_{42}$ monomers ($\text{mA}\beta_{42}$) and oligomers promote hippocampal LTP and reference and contextual fear memory dependent on $\alpha_7\text{NicRs}$ (Puzzo et al., 2008). Recent studies suggest that at low concentrations $\text{A}\beta$ oligomers (in the pM range) act as an agonist at $\alpha_7\text{NicRs}$ whereas higher concentrations negatively modulate $\alpha_7\text{NicR}$ function (Lasala et al., 2019). Recent studies by Puzzo's group show $\alpha\text{A}\beta_{42}$ in the mid-pM range signals through $\alpha_7\text{NicRs}$ to promote conversion of early LTP into late LTP and establishment of long-term memories (Gulisano et al., 2019). This pro-LTP effect was augmented by not only increased presynaptic transmitter release but of particular interest here, increased expression of several molecules involved in longer-term plasticity including CREB, CAMKII and BDNF, leading the authors to hypothesize a role of $\alpha\text{A}\beta_{42}$ in STC (Gulisano et al., 2019).

Variants in the $\alpha_7\text{NicR}$ gene associate with several dementias including AD and Pick's disease (see Feher et al., 2009 including reference to contradictory findings). Multiple studies show upward of pM concentrations of $\text{A}\beta$ impact $\alpha_7\text{NicR}$ functioning (Oz et al., 2013) and $\text{mA}\beta_{42}$ shows an unusually high affinity of low fM to low pM binding to $\alpha_7\text{NicRs}$, whereas $\alpha\text{A}\beta_{42}$ shows affinity in the low nM range (Cecon et al., 2019; Smith and Strittmatter, 2017; Wang et al., 2000a; Wang et al., 2000b). Puzzo (2015a) suggests $\text{A}\beta$ binding to nicotinic receptors increases synaptic plasticity and memory at physiological concentrations, switching to causing synaptic dysfunction at higher concentrations. However, as far as the author is aware, no studies have reported binding of $\text{A}\beta$ to the PRPC- $\alpha_7\text{NicR}$ complex and taken with the above, it may be that though $\text{A}\beta$, PRPC and $\alpha_7\text{NicRs}$ interact it may differ fundamentally from the interaction of PRPC with mGluR5. That said, absence of evidence is not evidence of absence - identification of mGluR5 as a coreceptor of PRPC was based on a screen of 81 known transmembrane PSD proteins able to activate Fyn of which $\alpha_7\text{NicR}$ was not included (Um et al., 2013). Studies directly addressing relationships between $\text{A}\beta$, $\alpha_7\text{NicRs}$ and PRPC may yet identify an interaction.

As will be discussed further (see section 18), $\text{A}\beta_{42}$ binds the p75 neurotrophin receptor (p75NTR), noteworthy as p75NTR is heavily expressed in basal forebrain cholinergic neurons. P75NTR has several significant interactions. Firstly, as introduced above, p75NTR inhibits $\text{A}\beta$ aggregation but also induces

structural alterations in dendritic spines and spine loss (Patnaik et al., 2020). P75NTR is a receptor of proBDNF where it acts to support LTD (see Korte and Schmitz, 2016) and studies suggest P75NTR supports repetition-dependent synaptic suppression (Sakuragi et al., 2013).

Evidence supports the possibility that PRPC and oA β impact NMDA signaling (see Hamilton et al., 2015; Stys et al., 2012). Co-precipitation studies show PRPC can form complexes with NMDARs (Khosravani et al., 2008; You et al., 2012) and one possible action may be to promote desensitization of NMDARs by decreasing affinity for glycine thereby protecting neurons from excessive NMDAR activation (You et al., 2012) as persistent overactivation may cause cell death (see Black et al., 2014; Stys et al., 2012). PRPC may also tune 5-HT signaling by modulating coupling of 5-HT₂ receptors to G-proteins in neurons, altering the distribution and activity of 5-HT_{1b} receptors and controlling cross-talk between 5-HT₂ receptor signaling (see Hirsch et al., 2014). Relatedly, PRPC KO mice exhibit a depressive phenotype (Beckman et al., 2015).

Taken together, these findings suggest that PRPC particularly could function as a critical point at which specifically oA β ₄₂ binds and modulates activity in post-synaptic neurons. As this effect is primarily one associated with LTD and depotentiation, oA β ₄₂ binding may serve to protect against over-excitation. In this sense, oA β ₄₂ binding to PRPC may “write-protect” post-synaptic neurons, guarding against interference that could potentially alter plasticity. **Figure 3** depicts a scheme of how this function of A β may operate. Increases in presynaptic excitatory activity responsible for upscaling synaptic strength through LTP occur coincident with release of mA β ₄₂ from presynaptic terminals. Initially, low concentrations of synaptic mA β ₄₂ promote LTP, possibly through α_7 NicRs activation. Simultaneously, release of excitatory transmitters, typically glutamate, induces LTP through various well-established mechanisms. As mA β ₄₂ levels build, mA β ₄₂ binds PRPC. Not only does the mA β ₄₂-PRPC complex encourage growth of oA β ₄₂ oligomers bound to PRPC but mA β ₄₂ in the extracellular space may undergo spontaneous self-oligomerization forming oA β ₄₂ also capable of binding to PRPC and other membrane receptors. The oA β ₄₂-PRPC complex then associates with various postsynaptic receptors, particularly mGluR5 where it sets in motion a series of intracellular events that act to ensure upscaled activity in the post-synaptic cell is protected. Relatedly, glutamate excitotoxicity is implicated in AD progression: increased glutamatergic activity in early stages transitions to glutamatergic hypoactivation coincident with depression of LTP and cognitive deficits at later stages; a sequence that has been proposed to be mediated by A β acting at presynaptic sites (Findley et al., 2019).

Though currently there is little published evidence exists to suggest this, the efficacy of PRPC-bound oA β ₄₂ to activate intracellular pathways may depend not only on oA β ₄₂ concentration but also on the size of bound A β ₄₂ oligomers. In fact, oA β ₄₂ may be more effective than mA β ₄₂ at promoting LTP at low concentrations and may even tend to remain in the oligomeric form (Gulisano et al., 2018). As concentrations of A β ₄₂ rise, A β ₄₂ that acutely acted to promote transmitter release (Koppensteiner et al., 2016; Puzzo et al., 2008) and synaptic LTP (Puzzo et al., 2008) transitions to restraining presynaptic transmitter release (He et al., 2019; Moreno et al., 2009), essentially isolating the post-synaptic cell from further synaptic input (**Fig. 3**). In this manner, the extreme stability of oA β ₄₂ and its high affinity binding to PRPC constitute a solid-state tag marking recruitment of potentiated synapses into wider circuits. Maintaining the potentiated state requires the synapse to be adequately supplied energetically. As the stability of oA β ₄₂ depends less on the local energetic environment, oA β ₄₂-tagging of synapses insures against short-term fluctuations in energy supply such as during hypoxia and ischemia, as well as long-term metabolic changes such as starvation and diabetes. As such, oA β ₄₂-tagging not only marks synapses as engaged, protecting them against attempts to delete or overwrite established plasticity but also

renders long-term memories as non-volatile, resistant to “power cuts” or insults that would otherwise threaten to undo established changes in plasticity.

Thus, PRPC may be a molecule (but possibly not the only one) crucial to wiring in the mnemonic properties of A β into molecular networks underlying homeostatic plasticity, synaptic scaling and STC. In further support of this synaptic tagging-like role of A β , recent studies by Li *et al* show APP/PSEN1 transgenic mice fail to transition late-LTP into metaplasticity, while showing no deficits in LTD. Additionally, these mice exhibit lowered levels of the PRP PKM ζ . Activation of ryanodine receptors re-establishes late-LTP and STC coincident with increases in PKM ζ (Li *et al.*, 2017a). As introduced above, such a scaling function of A β likely involves both pre-synaptic and post-synaptic mechanisms. But, fundamentally the role of A β in maintaining long-term changes in synaptic efficacy is predicted to be more managerial than mediatory, and this locking-in action likely requires interfacing with pathways involved in STC (**Fig. 2**). As introduced above, various intracellular molecules downstream of mGluR5 activation such as Arc and CAMKII are implicated in STC. (**Table 1**). Additionally, PRPC controls sprouting of neurites by stabilizing actin (Loubet *et al.*, 2012) and actin dynamics are under the control of Arc (Nikolaïenko *et al.*, 2018), a central hub controlling structural and homeostatic plasticity (Korb and Finkbeiner, 2011; Nikolaïenko *et al.*, 2018). Studies show Arc is a major downstream target of group 1 metabotropic receptors, mediating roles in LTD and synapse elimination (see Wilkerson *et al.*, 2018) and by reducing nuclear GluA1 transcription scales down synaptic strength (Korb *et al.*, 2013). eEF2, which is also downstream of mGluR5 (**Fig. 3**) is also implicated in long-term consolidation of memories (Im *et al.*, 2009).

Viewed as a write-protect tag it is conceivable that studies showing PRPC mediates “toxic” effects of oA β_{42} could at least partially be interpreted as oA β_{42} and PRPC serving an intended function of preventing overexcitation of post-synaptic cells. The counter-LTP and pro-LTD effects of oA β_{42} are often portrayed as undesirable effects, often associated with words such as “deficits”, “impairments”, “pathophysiological”, “neurotoxic” and “disruptive”. Indeed, throughout this text I too often use these words, often to stay in keeping with the interpretation made by the authors of the original articles. However, the notion that some of these effects may in fact be guarding against unwanted attempts to alter established synaptic efficacy or to ensure a pool of synapses are kept unpotentiated for future recruitment is, I believe, very much worth entertaining. Effects of oA β_{42} on spine stability (Brody and Strittmatter, 2018; Um *et al.*, 2012) and apoptosis (Hyeon *et al.*, 2012) may too be part of an intended program of synaptic and network refinement that underlies optimizing network efficiency either as part of normal physiology or in response to encroaching pathological threats. This is not to say by any means that oA β_{42} is never toxic (see section 21) - the evidence is virtually indisputable (Ferreira *et al.*, 2015; Huang and Liu, 2020; Reiss *et al.*, 2018). Rather, before achieving toxic levels, oA β_{42} performs important beneficial functions in maintaining long-term memory. If so, this would naturally lead to new questions: Exactly at what point does a beneficial physiological function of oA β_{42} transition to a toxic effect? What specifically causes oA β_{42} toxicity? To what degree is oA β_{42} acting directly toxic, and what other molecules transduce its toxic effects? What mechanisms exist to limit toxicity? What is the relationship between the physiological/pathological effects of oA β_{42} and other known players such as tau, ApoE, TREM2 and neuroinflammation? And perhaps, most importantly, are these effects reversible?

9. Molecular control of oA β_{42} -dependent modulation of memory

Supposing that oA β_{42} protects established changes in plasticity via PRPC one would expect the existence of mechanisms regulating this process. How could this occur? Whatever form this takes must ultimately

determine how much, how aggregated, and in which neuronal circuits A β controls synaptic efficacy, or how they respond to A β_{42} . “How much” is primarily determined by A β synthesis and clearance, which will be addressed further below (see end of this section). “How aggregated” depends on many factors, not just local A β concentrations, but also the ionic composition of the local medium, concentrations of metal ions such as zinc and copper, pH, temperature, the presence of other interacting molecules including APP derivatives, and even physical events such as vibration and head trauma. “Where” could be determined by many factors not limited to the expression of APP and A β binding sites on different cell types (e.g., glial, neuronal, epithelial); different localities (e.g., pre versus post-synaptic) and modulation of binding (e.g., by post-translation modifications of A β receptors). How cells respond to A β_{42} could be controlled by a wide range of mechanisms (many of which may be already known) that depend on the intracellular signaling pathways activated.

How could A β_{42} binding to PRPC be regulated and is this process reversible? One possibility is the co-chaperone protein, heat shock protein stress induced phosphoprotein 1 (STI1, **Fig.2**) (see da Fonseca et al., 2021; Lackie et al., 2017; Linden, 2017). STI1 coordinates 70 kDa heat shock proteins (HSP70) and 90 kDa heat shock proteins (HSP90) in the process of protein folding, both of which have been linked to neurodegenerative diseases (see Lackie et al., 2017). HSP70 itself is strongly implicated in memory and consolidation processes (see Karunanithi and Brown, 2015; Porto and de Oliveira Alvares, 2019) and alone in AD (Lu et al., 2014). Remarkably, intranasal administration of HSP70 extends the lifespan of aged mice while also improving cognitive function and synaptic physiology (Bobkova et al., 2015). HSP90 too is associated with protein folding/misfolding in neurodegenerative diseases (see Bohush et al., 2019; Luo et al., 2010). Interaction of STI1 with PRPC promotes formation of short- and long-term memories (Coitinho et al., 2007). Central administration of an STI1 fragment that includes the PRPC binding site improves age-related social recognition loss in mice (Rial et al., 2009). STI1 has a general neurotrophic effect being released from many cell types including astrocytes, promoting their own development via PRPC (Arantes et al., 2009). STI also promotes axogenesis in peripheral neurons via PRPC (Santos et al., 2013) and promotes neuritogenesis and neuroprotection in hippocampal neurons via PRPC (Lopes et al., 2005). This function depends on PRPC internalization (Caetano et al., 2008) and increased protein synthesis mediated by PI3K-mTOR (Roffe et al., 2010). STI1-PRPC interactions are neuroprotective, protecting cells against apoptosis (Lopes et al., 2005; Zanata et al., 2002). Though the exact signaling mechanism is unknown, STI1 is important in maintaining correct actin dynamics (Beckley et al., 2020). Critically, Ostapchenko and colleagues show upregulation of cortical STI1 in an AD mouse model and the brains of AD sufferers. oA β_{42} -induced synaptic loss and neuronal death and hippocampal long-term potentiation are prevented by STI1 administration (Ostapchenko et al., 2013). Blocking binding of STI1 to PRPC prevents oA β_{42} -induced toxicity and oA β_{42} binding to PRPC. Such an action could potentially impact signaling through any complex where PRPC acts as a co-receptor (Ostapchenko et al., 2013). STI1 interaction with PRPC also interacts with α_7 NicRs affording protection (Beraldo et al., 2010; Ostapchenko et al., 2013) and protects against oA β_{42} -induced toxicity (Maciejewski et al., 2016; Ostapchenko et al., 2013). Taken together, these studies suggest STI1 might limit the effects of oA β_{42} by modulating its interaction with PRPC.

That said, some findings may contradict such a conclusion. Overexpression of STI1 in mice *increased* BACE 1 activity, decreased matrix metalloproteinase 2 (an A β -regulating enzyme) activity, increased amyloid burden and induced memory deficits in the 5XFAD AD mouse model (Lackie et al., 2020a). However, concerns aside over the relevance of such an extreme AD model, STI1 is not postulated here to directly control A β turnover but rather modulate oA β_{42} interactions with PRPC. Overexpressing STI1 may increase extracellular A β_{42} levels by preventing oA β_{42} binding to a major physiological site of action causing A β_{42} to oligomerize in the extracellular space and reach neurotoxic levels. Furthermore,

compensatory increases in A β ₄₂ production may occur to counter loss of A β ₄₂ signaling through PRPC binding.

If STI1 is a major player in regulating A β ₄₂-PRPC interactions then how is STI1 itself controlled? STI1 lacks a signal peptide but studies show STI1 is released in exosomes along with PRPC (Hajj et al., 2013). Mice overexpressing STI1 show no overt cognitive or memory deficits (Beraldo et al., 2015) and a 50% reduction in wild-type STI1 levels produces only minor behavioral effects (Beraldo et al., 2015). On the other hand, mice expressing a hypomorphic STI1 allele exhibit age-dependent hippocampal neurodegeneration, reduced hippocampal volume and memory deficits (Lackie et al., 2020b). Though speculative, decreasing STI1 function may increase oA β ₄₂ binding to PRPC to lock memory circuits, which may manifest as memory deficits. Strengthening such a hypothesis requires further study and employment of models and paradigms conducive to understanding longer term memory.

Another potentially important PRPC interactor that may control PRPC-mediated A β effects is LRP/LR. This protein may in fact be the main cell surface receptor for PRPC (Gauczynski et al., 2001) and has remarkably diverse physiological roles in growth and survival. LRP/LR is particularly implicated in metastatic cancers, developmental diseases and neurodegenerative diseases (see DiGiacomo and Meruelo, 2016; Jovanovic et al., 2015) and has been suggested as a possible target for AD therapeutics (Jovanovic et al., 2015; Vana et al., 2009). LRP/LR binds and internalizes A β ₄₂ with a cytotoxic outcome, an effect reversed by downregulation of LRP/LR (Da Costa Dias et al., 2014). This effect depends on PRPC (Pinnock et al., 2016). LRP/LR appears to impact several aspects of APP processing including maturation and localization of APP (Bhattacharya et al., 2020). Fluorescence resonance energy transfer studies show LRP/LR directly interacts with γ -secretase and possibly indirectly with BACE to increase shedding of A β (Jovanovic et al., 2014). LRP/LR also directly interacts with pTau (Cuttler et al., 2020) and modulates A β toxicity (Bignoux et al., 2019). An intranasally administered antibody targeted to LRP/LR decreases A β plaques and improves memory performances in 5XFAD AD model mouse (Ferreira et al., 2018).

Like APP, PRPC undergoes α -secretase cleavage to shed secreted peptides neuroprotective against oA β ₄₂ through reduction of oA β ₄₂ binding to PRPC and bioactivity in the shed peptides (see Jarosz-Griffiths et al., 2019). PRPC might be released as its full length to serve a neuroprotective role following neurotoxic insults (Wang et al., 2012). PRPC also associates with LDL receptor related protein 1 (LRP1). LRP1 is necessary for mediating oA β ₄₂ toxicity (Rushworth et al., 2013) and A β clearance (see Kanekiyo and Bu, 2014). The LRP1, PRPC complex and tissue plasminogen activator (tPA) form a multimolecular complex driving neuritogenic signaling in response to tPA (Mattei et al., 2020). Aside from tPA being beneficial to A β clearance, tPA is associated with late phase LTP and LTD (see Lee et al., 2015). Overexpression of tPA strengthens and prolongs hippocampal LTP and improves learning (Madani et al., 1999). LRP1 is also a receptor of ApoE.

The above, while not exhaustive, illustrates some possibilities by which A β ₄₂ binding to PRPC could be modulated to ultimately impact longer term memory. Though the evidence is substantial, it is largely indirect and inferential. With this in mind, only directed study will provide supportive or contradictory evidence for the hypothesis that PRPC, or indeed any other A β ₄₂ receptor determines the permanence of long-term memories.

10. Control of A β aggregation

If indeed A β ₄₂ binding acts as a write-protect tag, an important question is, how refined and dynamic is this process? What controls association and dissociation of oA β ₄₂ with its receptors? Presumably, permanent irreversible binding of oA β ₄₂ would create an inflexible and perilous state, one that is difficult to imagine evolution has not guarded against. For example, binding of A β to insulin degrading enzyme (IDE) forms an exceedingly stable complex leading some to suggest that IDE acts as a “dead-end chaperone” that traps A β ₄₂ for controlled clearance (see de Tullio et al., 2008). Could the size of bound oA β ₄₂ determine the strength of the write-protect? If so, how could oligomers of different sizes be differentiated and acted upon? Or, does the potency of the tag depend on the number of A β binding sites? What would the ramifications of such highly stable binding be for memory and cognition?

oA β ₄₂ increases cell surface expression of PRPC (Caetano et al., 2011) and PRPC stabilizes oligomers in *Drosophila* models (Younan et al., 2018) and studies in mouse and human models show PRPC traps A β oligomers but only once misfolded, inhibiting fibril formation and even promoting their disassembly (Bove-Fenderson et al., 2017; Nieznanski et al., 2012; Younan et al., 2013). However, a consistent picture is yet to emerge as some studies show PRPC can promote conversion of fibrils into larger bundles (Nieznanski et al., 2014). Nonetheless, these findings suggest monomeric, oligomeric and fibrillar A β ₄₂ may exist in a dynamic equilibrium determined partially by the presence of PRPC. As synaptic mA β ₄₂ accumulates during neuronal activity, oligomers form, bind and stabilize on PRPC receptors, possibly confining PRPC to the cell surface. As mA β ₄₂ accumulates in the extracellular space, A β ₄₂ fibrils form and elongate. These may act either as local reservoirs of available A β ₄₂ and/or to prevent PRPC-bound oA β ₄₂ overly dampening activity in post-synaptic neurons and reaching neurotoxic levels. This might help explain why the presence of A β ₄₂ plaques poorly correlate with synaptic loss as this does not necessarily reflect A β ₄₂ reaching toxic levels.

For A β ₄₂ and other APP-derived peptides to effectively and safely serve functional roles their metabolism would need to be precisely regulated. Control of protein aggregation involves many factors including chaperone proteins, protein degradation by the ubiquitin-proteasome system, chaperone-mediated autophagy and macroautophagy, the unfolded protein response and compartmentalization into areas such as Q-bodies (see Ciechanover and Kwon, 2017; Mannini and Chiti, 2017; Stroo et al., 2017). Predicting, understanding and therapeutically manipulating A β ₄₂ aggregation will require thorough study of these processes. For instance, the chaperone clusterin (coded by the LOAD risk gene CLU) may influence A β ₄₂ aggregation bidirectionally depending on its relative concentration (see section 12.3 and Foster et al., 2019). Other chaperones implicated in AD include the heat shock proteins HSP60, HSP70 and HSP90 (see Campanella et al., 2018). Moreover, some of these chaperones interact with other AD-relevant molecules such as pTau (see Salminen et al., 2011).

Holding A β ₄₂ at a specific point along a monomeric-oligomeric-fibrillar-plaque continuum depends on environmental factors such as concentration, pH, ionic environment, presence of transition metals, temperature, mechanical stress (e.g., agitation, vibration) and interactions with surfaces such as cell membranes (see Almeida and Brito, 2020). Fluorescence correlation spectroscopy studies suggest the critical concentration at which mA β ₄₂ starts to form oligomers is around 90 nM (Novo et al., 2018), a concentration at the upper end of the pM to nM range found in brain compartments and around the estimated affinity of oA β ₄₂ for the PRPC and p75NTR receptors (see Smith and Strittmatter, 2017). However, it is not inconceivable that concentrations this high are achieved in the synaptic cleft or perisynaptic region, where for example, mGluRs are located. What is clear is that synaptic activity plays a direct role in A β homeostasis (see Tampellini, 2015) and changes in neuronal activity can directly influence A β aggregation, at least in AD mouse models (Yuan and Grutzendler, 2016).

It is timely to reiterate the importance of understanding the precise control of APP expression, trafficking, its differential commitment to the two major (amyloidogenic versus non-amyloidogenic) pathways and its catabolism. The catabolism and clearance of A β involves either enzymatic degradation or non-enzymatic mechanisms. Key enzymes involved in degradation include neprilysin, IDE, endothelin converting enzymes and cathepsin D (Baranello et al., 2015; Nalivaeva et al., 2014; Yoon and Jo). These enzymes typically have targets other than A β so understanding how their regulation fits in to the wider proteome is crucial to understanding their role in AD and their viability as therapeutic targets. In addition to enzymatic degradation, A β is also cleared by interstitial fluid drainage and drainage through the glymphatic system (see Jessen et al., 2015; Yoon and Jo, 2012) with recent studies in the 5XFAD mouse model interestingly showing this can be promoted by ultrasound (Lee et al., 2020). AD-sufferers exhibit reduced CSF levels of A β_{42} , an observation that confers this measure as a predictive biomarker, albeit not as well as the ratio of A β_{42} to A β_{40} (Hansson et al., 2019; Holtzman, 2011). However, why AD-sufferers show *lowered* rather than *raised* A β_{42} levels is at least *prima facie* perplexing (see Holtzman, 2011 for discussion). Possibilities include impaired clearance mechanisms or snowballing aggregation of A β_{42} in the brain that sequesters A β_{42} from the CSF.

Currently relatively little is known about the physiological control of A β clearance on a wider level. Recent studies show that the tryptophan metabolite 5-hydroxyindoleacetic acid (5-HIAA) and kynurenic acid regulate the activity of several metalloproteinases involved in A β degradation (Maitre et al., 2020). 5-HIAA is also a metabolite of 5-HT suggesting a means by which serotonergic transmission might regulate A β turnover. 5-HIAA administration decreases brain A β burden and improves memory impairments in AD model mice, possibly by increasing neprilysin levels (Klein et al., 2018). Other neuromodulators also appear to impact A β turnover. Lowered nitric oxide levels promote A β clearance (Ridnour et al., 2012). NE promotes microglial uptake and degradation of A β (Kong et al., 2010). Blocking NE flux, simulating the decreased NE activity occurring in sleep (Jessen et al., 2015) increases influx of CSF into the brain where it may aid A β clearance (Xie et al., 2013).

11. The risk factor ApoE

A well-established regulator of A β aggregation and clearance in the brain is the glycoprotein ApoE (Holtzman et al., 2012; Liu et al., 2013; Safieh et al., 2019). ApoE is synthesized particularly in the liver and mediates lipid transport between cells and tissues. Cholesterol is a major lipid regulated by ApoE and polymorphisms in the ApoE gene are associated with hypercholesterolemia a major consequence of which is susceptibility to atherosclerosis, coronary heart disease and stroke. In the brain, ApoE is constitutively expressed especially in astrocytes but also in microglia, vascular smooth muscle cells and the choroid. Neurons normally synthesize little ApoE but do so under stress.

APOE polymorphisms are the strongest known genetic determinant of risk in LOAD. Individuals carrying the $\epsilon 4$ allele are considerably more likely to develop AD and at a younger age, in addition to increased risk of amyloid angiopathy and as one might expect, age-related cognitive decline (Liu et al., 2013). In contrast, carriers of the $\epsilon 2$ allele benefit from some protection. Polymorphisms in ApoE are also one of the most consistent associations with lifespan (Brooks-Wilson, 2013). There is considerable evidence that ApoE polymorphisms impact A β metabolism with the $\epsilon 4$ allele reducing A β clearance, synaptic function and neurogenesis, and increasing A β aggregation and tangle formation. The $\epsilon 2$ allele protects against some of these effects (Liu et al., 2013; Safieh et al., 2019).

Given the hypothesis that receptor-bound $\alpha\text{A}\beta_{42}$ may constitute a write-protect tag, one might predict that dysregulation of $\text{A}\beta$ metabolism and clearance would impact cognition and mnemonic processes throughout life. That is, as $\epsilon 4$ carriers likely exhibit reduced clearance of $\text{A}\beta_{42}$ (Wildsmith et al., 2013) they may possess a larger available pool of free $\text{A}\beta_{42}$ from which to form write-protect tags. Extending this postulate to cognitive outcomes, one might predict that at younger ages before mnemonic circuits become oversaturated with $\text{A}\beta_{42}$, $\epsilon 4$ carriers might exhibit some of the following phenotypes: (1) be more predisposed to forming long-term memories either deliberately or unwillingly, (2) show less spontaneous memory loss or forgetting, (3) experience increased difficulty in modifying memories, which might be reflected in processes such as cognitive flexibility and (4) be more vulnerable to psychiatric disorders driven by aberrant memories such as PTSD and addiction.

If so, some of these differences may be reflected in measures such as educational attainment, measures of intelligence, career paths and socioeconomic status. However, the picture is mixed. Toddlers carrying the $\epsilon 4$ allele do perform better on the Bayley scales infant development score; a measure of brain development (Wright et al., 2003). However, children, especially girls, carrying the $\epsilon 4$ allele score lower on IQ tests (Reynolds et al., 2019) and young adult $\epsilon 4$ carriers have reduced hippocampal volume (O'Dwyer et al., 2012). Tuminello and Han argue and provide evidence that the $\epsilon 4$ allele may endow cognitive benefits in younger age groups, switching to detriment as individuals age (Tuminello and Han, 2011). For instance, some studies report young adult $\epsilon 4$ carriers as having better episodic memory and neuronal efficiency (Mondadori et al., 2007), as have other studies suggesting the $\epsilon 4$ genotype bestows improved memory for brief but not longer durations across lifespan (Zokaei et al., 2020), though there are reports that $\epsilon 2$ carriers have better short-term memory versus homozygous $\epsilon 3$ carriers (Zokaei et al., 2021). However, Tuminello and Han point out that studies supporting improved memory and cognition in young $\epsilon 4$ carriers are equally matched by studies showing opposite findings (see Tuminello and Han, 2011).

Numerous reports have focused on potential associations of ApoE genotype with cognition in healthy individuals though mostly these have studied individuals over 50 (see O'Donoghue et al., 2018; Salvato, 2015). As yet and again, a consistent pattern of findings has not emerged and meta-analyses indicate no major effects in older individuals (see Lancaster et al., 2017; Small et al., 2004) or younger people individuals (see Ihle et al., 2012; Weissberger et al., 2018). Taken together, there is currently no overriding evidence to suggest possessing the $\epsilon 4$ allele confers a cognitive advantage or disadvantage earlier in life. However, one might argue that the cognitive measures (e.g., processing speed, working memory) used in these analyses are unsuitable for supporting the hypothesis that variations in $\text{A}\beta$ metabolism impact longer-term or lifelong memory. That is, studies to date have not focused directly on cognitive measures where the most profound effects might be evident, such as very long-term memory and reversal learning. That said, studies to date have included measures such as educational achievement that one might expect to correlate with improved long-term memory skills, though here too no consistent association has been found (Weissberger et al., 2018).

On the other hand, given the prediction that $\alpha\text{A}\beta_{42}$ primarily serves to protect rather than establish plasticity underlying long-term memory, effects of ApoE polymorphisms on memory may not manifest until late in life when memory circuits approach capacity. Unfortunately, as yet very few studies have addressed longer term and lifelong memories. In a recent study of asymptomatic $\epsilon 4$ carriers in their 40 to 60s, ApoE status did not impact memory encoding or forgetting over a 30 min period. However, interestingly status was associated with forgetting a week later with increasing number of copies of $\epsilon 4$ being linearly detrimental (Zimmermann and Butler, 2018). Zokaei *et al* recently reported poorer long-term memory (20 minutes) despite possessing enhanced short-term memory, suggesting again that

ApoE status does not negatively impact encoding, and may even be beneficial, but consolidation to longer-term memory is impaired (Zokaei et al., 2019). Thus, it seems by the 4th or 5th decade of life, retaining memories over long but not short periods is more challenging to $\epsilon 4$ carriers. Findings such as these are not particularly unexpected as they support the general view that impaired A β clearance is somehow detrimental to forming new memories later in life. It is becoming increasingly clear that AD may be the end stage of what could be argued is a very slow non-linear cognitive decline starting somewhere around the mid 30s. Interestingly, combat-veterans carrying the $\epsilon 4$ allele are more likely to develop PTSD (Kimbrel et al., 2015). This might reflect formation of unusually strong and resilient long-term fear memories. However, interpretation of such studies can be confounded by physical injuries suffered by combat veterans. Nonetheless, PTSD sufferers are at higher risk of developing dementia (Yaffe et al., 2010) as well as premature senescence (Lohr et al., 2015), which might suggest a relationship between the strength or permanence of memories and overloading of memory circuits.

12. Other risk factors

For reasons of scope and space, I do not wish to make a comprehensive discussion of the many risk factors associated with AD. For this the reader is referred to AlzRisk database (<http://www.alzrisk.org>) and excellent recent reviews (Edwards Iii et al., 2019; Serrano-Pozo and Growdon, 2019; Silva et al., 2019). Nonetheless, in the sections that follow I focus on several risk factors particularly pertinent to the current discussion.

12.1. Educational attainment, mental and social engagement

Higher educational attainment is generally considered a positive risk factor for developing AD, all be the evidence somewhat inconsistent (Baumgart et al., 2015; Caamano-Isorna et al., 2006; Larsson et al., 2017; Livingston et al., 2020; Meng and D'Arcy, 2012; Sharp and Gatz, 2011). Interpreting relationships between epigenetic and acquired risk factors and phenotypes is difficult due to inter-correlation with related variables. Educational attainment is naturally impacted by and related to factors such as socioeconomic status, lifestyle, occupation, diet and health disparities. Nonetheless, success in education requires not only understanding but also committing large amount of information to memory at least over relatively long periods of time. One might speculate that those undergoing more education are less likely to develop AD because they are more efficient in memorizing information or simply possess more memory storage. Alternatively, individuals who undergo more education are better trained in exercising cognitive processes that benefit them in their senior years. A common interpretation of this correlation is that those partaking in more education have increased brain or cognitive reserve (Stern, 2009, 2012). Brain reserve generally refers to measurable differences such as number of neurons, synapses, extent of neurogenesis or brain size. The related concept, cognitive reserve, refers to a more emergent property of the degree to which the brain functions as an efficient and effective processor and information store. One possibility is that individuals attending more education do so because they are better “rememberers” due to increased information storage capacity. However, most people are formally educated in the early stages of their life long before memory circuits are likely to overload. More likely, these individuals have a combination of more efficient and accurate memory storage, higher intelligence, better attention, more motivation and any number of other related psychological processes that make them more likely to succeed in education. Conceivably, those with more cognitive reserve are so because their brains are more effective at using and regulating write-protection mechanisms conferred by A β_{42} accumulation.

It is also important to consider the nature of the information gleaned in education. That is, information transmitted through education such as concepts and facts is often compact and places relatively little burden on memory storage though it often requires strong understanding and reasoning. In contrast, information delivered through media such as the internet, video games, television and music may be more understandable but is relatively data rich, placing a far higher demand on memory storage. Though it may sound absurd, education may only protect against AD because it diverts individuals from activities that load the brain with large amounts of relatively “useless” information.

Increased engagement in complex mental activities throughout life also correlates negatively with dementia rates (Valenzuela and Sachdev, 2006). This also may be due to better or more efficient functioning of cognitive circuits due to increased or more flexible memory capacity. Put another way, individuals tend not to engage in activities they find mentally strenuous or overly challenging. Alternatively, or additionally, engaging in complex mental activity may re-engage and flex memory circuits allowing reminding, reinforcement or other modifications beneficial to their persistence. This might also include re-arrangement or compression of information to increase efficiency, offsetting increasing A β load. Similarly, modifiable risk factors such as social interaction, depression and even exercise (Baumgart et al., 2015; Livingston et al., 2020) may all impact re-engagement and refinement of memory circuits (see Nehls, 2016 for discussion). Interestingly, once diagnosed with MCI or AD, individuals with higher levels of occupational (Myung et al., 2017) and educational attainment (though see Paradise et al., 2009; Stern et al., 1999; Stern et al., 1995) respectively deteriorate faster. This supports a hypothesis whereby these individuals are better able to reorganize cognitive networks in the face of A β overaccumulation, but having reached the limit succumb to the disease more abruptly.

On a somewhat related note, a very small number of healthy individuals experiencing the condition hyperthymesia possess incredible long-term memory abilities. These individuals are capable of feats such as recounting autobiographical experiences from every day of their lives since early teen years. Other so-called “savants” display incredible skills of mental arithmetic, photographic memory, hyperlexia, calendar calculations, memorizing numbers (e.g., pi to 100,000 digits) or melody sequences (e.g., Mozart). Little is known about these “super rememberers” though imaging studies identify morphological differences in the inferior and middle temporal gyri, temporal pole, anterior insula, and parahippocampal gyrus (LePort et al., 2012). This leads one to ponder if such superior long-term memory relates to functional differences in the threshold for STC or over-write protection, and if so, does it impact functioning in other cognitive domains?

As yet, virtually nothing is known about the molecular or genetic characteristics of these individuals, but it is interesting to note that unusual mnemonic skills often present in autistics (Happe, 2018). Currently, there is little direct evidence to draw strong connections between autism, hyperthymesia and molecules associated with AD pathology. However, it is interesting to note that autism spectrum disorder (ASD) positively correlates with several measures that also correlate with decreased AD susceptibility including educational and occupational attainment (Crespi, 2016). Additionally, mutations in FMR1, the FMRP encoding gene, are highly associated with ASD (Hagerman et al., 2011). FMRP, as introduced above (see section 8) interacts downstream of group 1 mGluRs and has several known associations with actin dynamics, LTD, LTP and control of homeostatic plasticity (Mercaldo et al., 2009; Michaelsen-Preusse et al., 2018; Sidorov et al., 2013). Other overlaps in gene associations between AD and ASD include APOE, APP and BDNF (see Sokol et al., 2011) leading some to propose a framework where the two disorders are related specifically through overproduction of sAPP α in ASD (Sokol et al., 2011).

12.2. *TREM2*

Loss of function mutations in TREM2 are a risk factor in LOAD. TREM2 is a membrane protein expressed uniquely in microglia involved in immune and inflammatory responses. TREM is a receptor for A β ₄₂ mediating its uptake and degradation by microglia (Carmona et al., 2018; Deczkowska et al., 2020; Gratuze et al., 2018; Karanfilian et al., 2020; Ulland and Colonna, 2018; Wolfe et al., 2018; Yeh et al., 2016; Zhao et al., 2018; Zhong and Chen, 2019), in addition to being a receptor for many lipoprotein particles and apolipoproteins some of which are implicated in AD including low-density lipoprotein (LDL), very low density lipoprotein (VLDL), high-density lipoprotein (HDL), APOE and CLU (Wolfe et al., 2018; Yeh et al., 2016). Binding of A β ₄₂ to TREM2 induces microglial activation, proliferation, migration, apoptosis and expression of pro-inflammatory cytokines. As neuroinflammation is a common pathology found in AD there has naturally been a great deal of interest in TREM2 as a pathological cause and therapeutic target (Carmona et al., 2018; Deczkowska et al., 2020; Karanfilian et al., 2020; Ulland and Colonna, 2018; Zhong and Chen, 2019). In addition to clearing A β , TREM2 may regulate A β aggregation (Parhizkar et al., 2019) and as such regulate synaptic plasticity. The notion that glial cells are important to maintaining memory circuits is far from unfamiliar given their role in sustaining excitatory-inhibitory balance in the brain through regulation of extracellular glutamate and GABA levels (Fellin et al., 2006; Henstridge et al., 2019; Mederos and Perea, 2019). Indeed, other have emphasized the role of glial cells in mediating tau-induced impairments of neuroplasticity (Koller and Chakrabarty, 2020). For instance, astrocytic Gs-coupled signaling controls long-term memory independent of learning via astrocytic Adora2A receptors. Genetic removal of these receptors increases Arc expression and reverses the memory deficits in AD model mice (Orr et al., 2015).

Microglial TREM2 may also regulate long-term plasticity as TREM2 controls synaptic refinement during development (Filipello et al., 2018; Jay et al., 2019). Relatedly, studies show reactivation of neurodevelopmental synaptic pruning pathways by the complement system in AD (Hong et al., 2016) (see Luchena et al., 2018) leading one to speculate that TREM2 may be central to experience-dependent structural plasticity dependent on A β . In support, recent studies find aged TREM2 KO mice exhibit enhanced synaptic plasticity and cognitive function (Qu and Li, 2020); an effect that may be due to decreased clearance of A β ₄₂ performing a beneficial action. Other studies suggest complement C1q marks pTau containing synapses for microglial engulfment (Dejanovic et al., 2018). TREM2 is a substrate of γ -secretase (Glebov et al., 2016), which itself is under regulation of β -adrenergic receptors (Ni et al., 2006) indicating the possibility that NE controls learning via TREM2. Generally, there have so far been few studies directly addressing the role of TREM2 in neuroplastic process, though there is abundant circumstantial evidence that TREM2 may play an active role in tuning mnemonic processes (Karanfilian et al., 2020).

12.3. Clusterin

The third strongest established genetic risk factor for LOAD is the extracellular chaperone clusterin (CLU), also known as ApoJ. CLU is involved in clearing cell debris, protein aggregation and cell death and survival (Foster et al., 2019) and binds A β determining its aggregation and clearance. Whether or not CLU acts in a neurotoxic or neuroprotective fashion by increasing A β or decreasing A β clearance is unclear (see Foster et al., 2019). Evidence suggests that the specific capacity in which CLU acts depends on its concentration relative to A β , favoring A β aggregation when CLU is at very low relative concentrations, switching to inhibiting A β aggregation as CLU concentrations increase (Yerbury et al., 2007). An identical profile of effects is seen for α -syn (Yerbury et al., 2007). As far as the author is aware there is no evidence linking CLU activity directly to long-term neuroplasticity. However, CLU regulates NF- κ B (Santilli et al., 2003), which itself is implicated in adult neurogenesis (Bortolotto et al., 2014; Zhang and Hu, 2012), structural neuroplasticity and formation and extinction of long-term memories (Kaltschmidt and Kaltschmidt, 2015; Yang et al., 2012). CLU also inhibits aggregation of β 2-microglobulin

(Yerbury et al., 2007), a pro-aging factor detrimental to cognitive function (Smith et al., 2015) and may be involved in synaptic scaling (Goddard et al., 2007).

14. A system-wide view of A β -write protection of memory and its interaction with sleep

The central hypothesis presented here is that A β_{42} aggregates are critical to preserving synaptic efficacy in a particular state. In doing so, oA β_{42} maintains and protects neuroplasticity underlying memory. An event that is particularly important to establishing long-term memories is sleep. Though a full review of the topic is beyond the scope of the current text (see Born and Wilhelm, 2012; Diekelmann and Born, 2010; Klinzing et al., 2019; Rasch and Born, 2013), a brief introduction is warranted before embarking on detailing a system-wide view of the role of A β in protecting memory and the necessity of sleep.

A commonly held model is that sleep is necessary for sorting, consolidation, reorganization and integration of short-term memories into long-term memories. Generally, this involves establishing a representation of hippocampal-based short-term memories acquired during wakefulness as long-term memories in the neocortex during sleep. Sleep deprivation profoundly and negatively disturbs long-term memory formation and other cognitive functions such as attention and executive functioning (Lowe et al., 2017) and even very short naps can improve memory retention (Ficca et al., 2010). Sleep solves a particular problem faced by the brain – if, where and how to store the massive amounts of information it assimilates during waking periods. This information is derived mostly from recent sensory experiences but can also be generated internally through introspection, reasoning, deduction and mental rehearsal. Long-term storage of information must be achieved without overwriting or corrupting already stored information while allowing new learning – a problem called the “stability-plasticity dilemma” (Abraham and Robins, 2005). New short-term memories are formed largely during the waking state (though they may also be made during sleep such as memorable dreams). New sensory experiences are ongoing events, the relevance and meaning of which may not be immediately clear. Selecting from and appropriately integrating new short-term memories into established long-term memories requires a meticulous computation that can only be made appropriately once their relevance is clear. Sleep solves this problem by taking the brain “offline” while it performs a meta-analytic determination of if and how new memories should be classified, arranged and stored, a process required for “synaptic homeostasis”, which as Tononi and Cirelli suggest, is the “price of plasticity” (see Tononi and Cirelli, 2014). This process demands huge processing power, energy demands and thorough reference to established memories. It also may help prevent corruption of long-term memories by isolating the brain from further sensory information in the same way it would be unwise for two independent editors to attempt to modify the same document concurrently. Interestingly, recent studies by the Tonegawa group indicate that memories are formed simultaneously in the hippocampus and neocortex, which respectively weaken and strengthen as memories mature (Kitamura et al., 2017). Indeed, the prefrontal cortex plays an important role in processing short-term memories by focusing attention on relevant sensory representation and selecting information relevant to ongoing cognitive processing (see \Lara, 2015 #1405}. Thus, the loci of short- and long-term memory is not as simple as a hippocampus versus neocortex distinction and so all areas may require functional isolation from sensory input to accurately complete the task of long-term memorization without interference. Importantly, sleep also protects short-term memory from overloading. To aid with this, much of what is experienced during wakefulness is not stored with high fidelity. Rather the gist of experiences is stored with increasingly detailed long-term memory traces being formed through repeated exposure and reinforcement.

A β plaques materialize in a stereotypic spatiotemporal pattern during AD progression. Amyloid deposition starts in neocortical areas before incorporating allocortical areas (entorhinal cortex, hippocampal formation, cingulate cortex, amygdala) and limbic areas. In later stages, subcortical structures such as the striatum and areas of the diencephalon, brainstem and cerebellum are also incorporated. This cumulative pattern of A β deposition is consonant with the hypothesis that oA β_{42} tags and protects neuroplastic changes underlying memory, particularly declarative memories. That is, as experiences increase beyond storage capacity, problems first arise in the frontal and temporal cortex – the area of long-term memory storage. This is not to say that oA β_{42} may tag *only* neocortical memories. Indeed, oA β_{42} likely tags and protects newly generated hippocampal plasticity but as will be discussed, because the hippocampus may be flushed of A β_{42} with the diurnal sleep/wake cycle, the hippocampus is not the first area of pathological oA β_{42} deposition. Though the hippocampus is associated with forming and holding short-term memories, memories of experiences acquired over a whole waking period may need to reside in the hippocampus for 18h or more. During sleep, hippocampal memories are integrated into neocortical areas for long-term storage. Following, oA β_{42} -protected hippocampal synapses may be designated for re-use by removal of oA β_{42} -write protection (a process that may involve adult neurogenesis, see section 19) and so in healthy brains oA β_{42} does not accrue in the hippocampus. Supporting this, microdialysis studies in mice show increases in striatal and hippocampal interstitial A β_{42} levels during wakefulness and decreases during sleep (Kang et al., 2009; Roh et al., 2012). Similar diurnal variations in A β_{42} levels are observed in the CSF of humans (Bateman et al., 2007; Huang et al., 2012) with the amplitude of this variation decreasing with increasing age along with general increases in A β_{42} (Huang et al., 2012). The clearance of A β_{42} from the brain depends on the glymphatic system (Jessen et al., 2015), which occurs during sleep (Xie et al., 2013). The blunting of the A β_{42} cycle amplitude on a gradually increasing background may reflect a progressively decreasing dynamic range for oA β_{42} -synaptic tagging as neocortical memory circuits become overloaded and baseline A β_{42} levels increase. Sleep deprivation increases interstitial A β levels in mice (Kang et al., 2009) and a *Drosophila* AD model (Tabuchi et al., 2015). Similarly, sleep deprivation increases A β burden in humans, and remarkably this increase is specific to the hippocampus and thalamus (Shokri-Kojori et al., 2018). Concordantly, daily fluctuations in A β are lost following plaque formation in AD model mice and prominently reduced in young adult humans with presenilin mutations after plaque formation (Roh et al., 2012).

Together, these observations are consistent with the symptomology of AD based on the etiological hypothesis presented here (**Fig. 4**). In the early stages of AD memory loss is for recent events such as appointments and where objects were placed. At this point previously established long-term memories are intact and accessible with relatively little difficulty. This anterograde amnesia reflects the inability of newly acquired memories held in the hippocampus to be integrated into long-term memory due to saturation of long-term storage capacity. In support of this, recent studies find that new learning is more impaired rather other aspects of memory in the early stages of AD (Lim et al., 2020). As the disease progresses, A β deposits form along the allocortical-neocortical axis as attempts at consolidating long-term memories into the neocortex fail (**Fig. 4**). This manifests in what has been proposed as imbalance between firing stability and synaptic plasticity in cortico-hippocampal circuits driving the disease (Styr and Slutsky, 2018). The result is A β_{42} accumulation in the hippocampus as A β_{42} also temporarily write-protects recently acquired short-term memories until they are cleared from the hippocampus. As neocortical circuits saturate the brain is simply at a loss as to where to offload short-term memories, leaving them to accumulate and overload the hippocampus, causing anterograde amnesia.

Around this stage, over-deposition of oA β_{42} interferes with hippocampal memory indexing – a proposed function of the hippocampus to retain an index of long-term memories stored in neocortical regions (Teyler and Rudy, 2007). The hippocampal index functions like the index cards in a library cataloging

system, or the file allocation table of a computer memory system, pointing the hippocampus to specific engrams stored in the neocortex so they may be found on presentation of appropriate cues. Degeneration of the indexing system produces not only profound retrograde amnesia but also confusion as engrams are partially or incorrectly recalled from neocortical networks. Additionally, long-term memories may also become corrupted by incomplete or incorrect integration of new memories. This may render them inaccurate, improper or even absurd even though they are absolutely plausible to the individual. This causes confusion, anger, frustration, delusions, paranoia and even hallucinations in the patient. At this end stage, it is plausible that some long-term memories, especially those that are rarely-accessed are actually intact and uncorrupted. However, hippocampal dysfunction now renders them inaccessible, or if accessible, only partially, fragmented and uninterpretable. With the correct cues and depending on daily fluctuations in network stability, some of these memories may occasionally be recalled intact with surprising lucidity (Palop et al., 2006). Engramic representations of memories that were stamped in particularly hard due to their emotional valence may survive better than emotionally-bland memories. Thus, memories associated with for example fear, romance, nostalgia and happiness may persist better. Interestingly, a cue that may be particularly potent for accessing apparently lost memories is that of music – it is surprising how individuals can remember the melody and lyrics of music they may not have heard for decades. Anecdotal reports of otherwise unresponsive dementia sufferers spontaneously singing along to music exist (e.g., Music & Memory, 2011; Reed, 2015) and direct studies show exposure to self-chosen versus investigator-chosen music prompts better memory recall in AD patients (El Haj et al., 2015). As Sacks notes, familiar music gives “the patient access once again to moods and memories, thoughts and worlds that had seemingly been completely lost.” (Sacks, 2007).

Sleep is a multistage process comprising oscillations between four stages of slow wave sleep and REM sleep. REM sleep particularly is characterized by intense brain activity characterized by EEG recordings resembling the waking state. Though not limited only to this stage, REM sleep is when most vivid dreams occur which reflect the processing and long-term consolidation of memories, often those acquired during the prior waking period. Dreams often center around recent thoughts and experiences replayed with various degrees of fidelity and abstraction though specifically what type of memories undergo consolidation in REM sleep is not entirely clear (see Rasch and Born, 2013). As yet, no studies have reported a high-resolution analysis of A β clearance through various sleep stages though several related reports suggest a relationship. For instance, disruption of slow wave sleep associates with higher CSF A β levels (Ju et al., 2017) and AD model mice experience more slow wave sleep (Bentham et al., 2020). AD sufferers often exhibit sleep disturbances and alterations in sleep structure though a full review is beyond the scope of this discussion (see Cordone et al., 2019; Holth et al., 2017; Ju et al., 2014; Winsky-Sommerer et al., 2019). However, it is reasonable to speculate that sleep disturbances may relate to rhythms of hippocampal A β buildup and clearance coordinated with specific sleep stages as the brain processes, organizes and consolidates recently acquired short-term memories. Importantly, sleep is a carefully regulated process that has a bidirectional relationship with A β (see Cordone et al., 2019) and as will be discussed shortly (see further in this section), studies are starting to elucidate how A β regulates the sleep-wake cycle. For instance, recent studies show that ApoE ϵ 4 associates with longer sleep duration in cognitively impaired elderly individuals (Basta et al., 2021). Whether or not this is a direct interaction is unclear as interactions between sleep and polymorphisms in genes determining lipid metabolism are widespread (Noordam et al., 2019).

The key point here is that sleep allows the brain the opportunity to undergo cognitive reorganization and memory consolidation, which involves freeing of temporarily oA β ₄₂-tagged hippocampal circuits and creation and modification of neocortical oA β ₄₂-write-protected long-term memories. The process of dreaming is likely to be integral to and a reflection of this process. Memories of dreams recalled on

waking are often vivid and detailed yet ephemeral and rapidly forgotten. This nature of dreams may reflect deliberate disposal of temporary changes in plasticity underlying the narrative of the dream made only for the purpose of reorganization, thus preventing wastage of storage capacity and confusion with reality. This may explain why sleep disturbance are a risk factor for AD (Minakawa et al., 2019) and why increased daytime napping is found in the elderly. The confusion that characterizes “sundowning” in AD-sufferers may reflect reduced short-term memory capacity necessitating more frequent bouts of sleep for processing, consolidation and A β clearance from the hippocampus. Additionally, it is possible to envisage a vicious cycle whereby lack of sleep promotes buildup of A β , leading to poor sleep quality, then promoting further A β buildup. Hippocampal buildup of oA β ₄₂-tagged plasticity may also explain why “mentally exhausting” activities such as driving a car over a long distance are sleep-inducing despite little physical exertion. These activities require intense concentration and unavoidable exposure to massive amounts of novel information of which a surprising amount is stored in short-term memory regardless of whether one wishes to or not. For instance, subjects shown 2,560 photographs for 10 sec each in a single trial are able to correctly recognize over 95% of them when tested three days later (Standing et al., 1970), exemplifying the sheer capacity of the brain for storing information with even very brief exposure.

15. Norepinephrine modulation of learning and A β deposition

Sleep is governed largely by hypothalamic nuclei and a collection of brainstem nuclei known as the ascending reticular activating system, many of which broadcast isodendritic neuromodulators throughout the brain that regulate neuronal excitability and plasticity. Notable among these is NE released from locus coeruleus (LC) neurons, which also modulates processes central to learning such as vigilance, arousal and attention. Despite its profound influence over the brain, the LC is a remarkably small nucleus, estimated as having a little under 50,000 neurons in humans (Sharma et al., 2010). However, these neurons project monosynaptically and widely with the exception of the basal ganglia (Foote et al., 1983). The LC is almost completely inactive during REM sleep, which appears to be necessary for memory consolidation (Swift et al., 2018). The activity of NE neurons (and several other monoamine neuromodulators involved in arousal and learning such as histamine and 5-HT) are controlled by the sleep-related neuropeptide orexin (hypocretin), a hypothalamic neuromodulator promoting arousal and appetite (Inutsuka and Yamanaka, 2013). Dysfunctions in orexin transmission underlie narcolepsy, a disorder characterized by overwhelming daytime drowsiness and sudden bouts of sleep.

Evidence suggests a functional relationship between orexin, norepinephrine, A β and neuroplasticity though details are still emerging. Orexin-A administration, which activates NE neurons, increases interstitial A β levels in the hippocampus (Kang et al., 2009) leading others to speculate that orexin drives diurnal rhythms in A β (Cheng et al., 2014). However, deliberate degeneration of LC neurons using the neurotoxin DSP-4 increases A β plaques in an AD model mouse suggesting NE also promotes A β clearance (Kalinin et al., 2007). NE promotes microglial uptake and degradation of A β ₄₂ (Heneka et al., 2010; Kong et al., 2010) while β -adrenergic stimulation promotes production of A β via activation of γ -secretase (Bussiere et al., 2017; Thathiah et al., 2013). Enriched environments, which have many pro-cognitive effects, protect against A β toxicity via activation of β ₂-adrenergic signaling and moreover oligomeric A β inhibits and induces internalization of β ₂-adrenergic receptors suggesting a mechanism by which A β buildup acts to tone down learning (Li et al., 2013).

A direct relationship between NE and A β metabolism is supported by other studies. NE directly interacts with A β to prevent aggregation while also destabilizing A β fibrils (Zou et al., 2019). The physiological purpose of this is unclear but intriguingly agrees with studies showing that another pro-cognitive and pro-wakefulness agent, caffeine, has the same destabilizing effect (Gupta and Dasmahapatra, 2019). Relatedly, though some meta-analyses suggest trends towards beneficial effects of caffeine in AD (Santos et al., 2010), a recent analysis found no effect of coffee consumption in AD sufferers (Larsson and Orsini, 2018). That said, meta-analyses find caffeine consumption to be a positive risk factor for mortality (Crippa et al., 2014; Kim et al., 2019; Loftfield et al., 2018) so though caffeine consumption may not impact the progression of AD specifically, it appears to extend lifespan. Taken together, it seems that NE stimulates A β turnover by promoting A β release, preventing oligomerization and increasing clearance. Such increases in turnover could be related to A β involvement in learning-related activity during wakefulness.

If LC NE promotes wakefulness and consequent accumulation of receptor-bound A β in short-term learning areas of the brain, a pertinent question would be, how does the brain sense A β levels and does NE transmission mediate responses to excessively high A β levels? A simple and convenient explanation would be that the LC directly or indirectly senses increasing free or receptor-bound A β levels and responds by decreasing its own activity to allow transition into sleep. That the brain can sense A β levels is supported by recent studies in zebrafish showing A β acutely and reversibly induces sleep *dependent* on oligomer size in the absence of neurotoxicity: small oligomers promote wakefulness via β_2 -adrenergic receptors and progesterone receptor membrane component 1 whereas large oligomers promote sleep via PRPC (Ozcan et al., 2020). As such A β oligomers may act as throttle and brake, directing the brain into arousal and open to acquiring new information when small but braking learning as oligomers grow. Indeed, others have suggested that LC NE neurons control brain activity and A β levels, shutting down activity as A β accumulates (Ross et al., 2015). In support of this acute administration of soluble A β_{42} (presumably monomeric and small oligomers) increases brain NE content (Morgese et al., 2015) though whether or not this reflects increased extracellular levels is unknown.

Interestingly, the ability of A β oligomers to induce sleep depends on PRNP signaling (Del Gallo et al., 2020; Ozcan et al., 2020) and can be blocked by inhibiting signaling through the PRPC-mGluR5-Fyn cascade (Ozcan et al., 2020). Group 1 metabotropic receptors are implicated in sleep where in concert with the PRP Homer1a they scale down synapses during sleep to re-establish synaptic homeostasis (Diering et al., 2017; Martin et al., 2019). Such an action would be concordant with the notion that sleep is a period in which hippocampal plasticity established during wakefulness is essentially wiped after short-term memories are fully organized and consolidated into long-term memory networks outside of the hippocampus, thus making way for new plasticity in future waking periods. There has been a long-standing interest in the role of PRPC in sleep particularly as mutations in PRPC cause the prion disease fatal insomnia. PRPC regulates sleep and circadian rhythmicity (Roguski and Gill, 2017) and mouse studies indicate roles in governing sleep cycles and regulating sleep after periods of sleep deprivation (Dossena et al., 2008; Tobler et al., 1997).

These studies are interesting not only in the context of the prediction that A β may control the sleep-wake cycle but also that mechanisms able to detect increasing A β oligomerization may exist. Interestingly, human imaging studies find that mediofrontocortical A β burden correlates with impairments in non-REM slow wave activity, which appears to act as a mediator of poor overnight memory consolidation and hippocampal-neocortical memory transformation (Mander et al., 2015). These impairments in sleep and memory consolidation may reflect an inability of the brain to transform

short-term memories into long-term circuits due to lack of availability of non-oA β_{42} -tagged neurons in mediofrontocortical areas.

The function of brain NE is not limited to arousal but includes attention, vigilance, cognitive control and stress responses. As introduced above, experiences eliciting emotional reactions such as surprise, pleasure, fear and anxiety are readily learned. The imbuing of these experiences with affective and emotional reactions is embodied in their salience and heavily involves monoamine neuromodulators such as NE and dopamine (see Duzkiewicz et al., 2019; Ranjbar-Slamloo and Fazlali, 2019; Tully and Bolshakov, 2010). Blocking NE transmission with drugs such as propranolol interferes with the consolidation and reconsolidation of emotionally salient memories (Kindt and Soeter, 2018; Loneragan et al., 2013). Dysfunction in NE transmission is associated with AD (see Chalermmpalanupap et al., 2013; Gannon et al., 2015; Peterson and Li, 2018; Ross et al., 2015; Trillo et al., 2013) and polymorphisms in the β_2 -adrenergic receptor gene (ADRB2) have also been linked to AD (Yu et al., 2008b). A pro-arousal and anti-aggregating effect of NE may be in fitting with the well-established role of NE in learning emotionally salient events. Permission to code these events by NE acting via β -adrenergic receptors activates an intracellular cascade involving PKA and CAMKII ultimately regulating AMPAR trafficking to promote changes in synaptic efficacy (Hu et al., 2007) (see Hagena et al., 2016; Nguyen and Connor, 2019; Tully and Bolshakov, 2010). A β may promote this process by increasing post-synaptic excitability by directly binding to β -adrenergic receptors (Wang et al., 2010a).

16. Tau

16.1. *Tau pathology*

Hyperphosphorylation and aggregation of tau, like A β aggregation, has long been viewed as neurotoxic and pathological event. Indeed, there is plenty of evidence that accumulation of pTau drives a neurodegenerative process not just in AD but in other so-called tauopathies such as corticobasal degeneration, primary age-related tauopathy, progressive supranuclear palsy and tau-positive frontotemporal dementia with parkinsonism (FTDP-17). The relationship, if any, between A β aggregation and tau aggregation has been any area of major focus in the AD field in recent years. At risk of oversimplification, the prevailing view is that phosphorylation and aggregation of tau is the real perpetrator of neurodegeneration, which occurs downstream of A β aggregation (see Bloom, 2014; Jadhav et al., 2015; Kametani and Hasegawa, 2018; Luan et al., 2013; Musiek and Holtzman, 2015; Stancu et al., 2014). However, the relationship is far from clear and continues to stimulate much discussion. For example, transgenic AD mouse models harboring only expression of mutated human genes related to APP metabolism and A β production show little evidence of NFTs and little neurodegeneration (Drummond and Wisniewski, 2017). A β_{42} -induced impairment of long-term, but not short-term, synaptic plasticity and memory is unchanged by suppressing tau (Puzzo et al., 2020) and experimental tau phosphorylation can *protect* against A β -induced neuronal death (Ittner et al., 2016). On the other hand, important evidence pointing to pTau as the toxic agent comes from studies showing that progression of tau pathology through the brain in AD correlates better temporally and spatially with neuronal and cognitive deficits than A β deposition (Crespo-Biel et al., 2012; Jadhav et al., 2015).

Strikingly, one of the very first places in which pTau accumulates in AD is in LC NE neurons and the transentorhinal cortex, starting as early as the fourth decade of life long before cognitive impairment (Chalermmpalanupap et al., 2017; Weinshenker, 2018). Nonetheless, LC neurons die only during the later stages of the disease (Theofilas et al., 2017) and as introduced above, this degeneration is implicated in the memory deficits (see Chalermmpalanupap et al., 2013; Gannon et al., 2015; Giorgi et al., 2017;

Peterson and Li, 2018; Trillo et al., 2013). A particularly germane question is, why does this very discrete nucleus, along with other isodendritic neuromodulators, with such important associations to learning and memory accumulate pTau first? The answer might be found by reflecting and speculating on the physiological function of tau in the brain.

Tau protein is an intracellular protein discovered as a molecule promoting self-assembly and stabilization of microtubules (see Barbier et al., 2019; Mietelska-Porowska et al., 2014; Morris et al., 2011; Wang and Mandelkow, 2016). The accepted dogma is that by binding to microtubules, tau stabilizes their structure in addition to regulating organelle transport (Guo et al., 2017). Generally, phosphorylation of tau decreases the affinity of tau for microtubules. The so-called “hyperphosphorylation” of tau evident in AD and other tauopathies is believed to cause the microtubular network to disintegrate leading to cellular toxicity (Alonso et al., 2018; Bloom, 2014; Iqbal et al., 2010; Mietelska-Porowska et al., 2014; Morris et al., 2011; Wang and Mandelkow, 2016). Simultaneously, free hyperphosphorylated tau assembles into aggregates that themselves are believed to be neurotoxic. This narrative, which is built upon an immense amount of evidence has driven preclinical research and clinical development for many years, particularly as clinical developments centered around modulating A β and production have fared very poorly (Mehta et al., 2017; Yiannopoulou et al., 2019). The very fact that neurodegeneration occurs in some tauopathies in the absence of A β deposition certainly suggests pTau as potentially toxic and capable of acting independently of A β . However, it is worth pointing out that some of the most oft-cited evidence that pTau is *a* and *the* neurotoxic agent in AD is largely due to the stronger *correlation* of tau neurofibrillary pathology with cognitive impairments (Crespo-Biel et al., 2012; Jadhav et al., 2015). Arguably, at least some of this evidence could be interpreted as pTau only being found on the scene of distressed neurons, even playing neuroprotective roles and like much of the AD field, the narrative that pTau, particularly NFTs, is the *primum movens* in AD does not exist without some controversy (Bretteville and Planel, 2008; Castellani et al., 2008; Congdon and Duff, 2008; Cowan and Mudher, 2013; Gotz et al., 2008). For instance, it is not perfectly clear whether phosphorylation of tau occurs before or after detachment from microtubules (see Kent et al., 2020). APP knockout mice expressing a human mutant form of tau have surprisingly more, rather than less, NFTs (Vanden Dries et al., 2017). Evidence such as this (comprehensively reviewed in Cowan and Mudher, 2013) has led several authors to question whether pTau and aggregated tau are toxic, protective or neither (Bretteville and Planel, 2008; Castellani et al., 2008; Congdon and Duff, 2008; Cowan and Mudher, 2013; Gotz et al., 2008). An alternative view redolent of that instanced of A β is that only smaller aggregates of pTau are toxic, which form NFTs as a means of sequestering pTau into a form incapable of interfering with cellular metabolism (Castellani et al., 2008; Cowan and Mudher, 2013; Luna-Muñoz et al., 2013).

16.2. Could hibernation hold the key to understanding tau function in memory persistence?

Though most tau protein is bound to microtubules in axons, roles of tau in modulating actin dynamics and interactions between microtubules and actin have been suggested since the 80s (Cabrales Fontela et al., 2017; Elie et al., 2015; Frandemiche et al., 2014; Griffith and Pollard, 1982; Selden and Pollard, 1986; Sobue et al., 1985). The list of known tau binding partners is extensive including, of note, several Src-kinases including Fyn, STI1, PRNP, GSK3 β , calcineurin, calmodulin, Grb2, PIN1 (an isomerase linked with PKM ζ activity), HSP70, HSP90, APP, APOE, CLU, presenilins and α -syn (see Gunawardana et al., 2015; Mandelkow and Mandelkow, 2012; Trushina et al., 2019). In fact, the last four decades has revealed tau as functioning well beyond microtubule stabilization, exhibiting roles in axonal transport, neuronal plasticity, DNA protection, glucose metabolism and neurogenesis (see Barbier et al., 2019; Guo et al., 2017; Kent et al., 2020; Mietelska-Porowska et al., 2014; Morris et al., 2011; Sotiropoulos et al., 2017;

Wang and Mandelkow, 2016). Some suggest tau acts as a scaffolding protein (see Mietelska-Porowska et al., 2014; Morris et al., 2011), for example, tethering Fyn to PSD95/NMDAR signaling (Ittner et al., 2010).

The role of tau in hibernating animals may be especially informative to understanding its natural function. Hibernation is a natural phenomenon that helps animals survive extreme environmental conditions of cold and food scarcity by minimizing energy expenditure. During hibernation, animals enter a state of torpor associated with huge decreases in heart rate, oxidative metabolism, oxygen consumption and reductions in cerebral blood flow. Despite brain temperature falling to within just a few degrees above ambient temperature, true hibernators awake from torpor without brain damage. A major challenge faced by hibernators is how to “power down” the brain down without damaging neurons and maintaining established changes in synaptic plasticity (i.e., memories) formed between bouts of torpor. For instance, the ability of Golden hamsters to recall a maze is maintained through hibernation (Bullmann et al., 2016), and though memories may not always survive without some impairment, evidence suggests that they are not totally lost (see Horowitz and Horwitz, 2019). Indeed, losing these memories would be perilous, particularly as some hibernators such as hamsters and chipmunks cache food.

How hibernators achieve this amazing task despite massive decreases in neuronal activity may depend on tau. Here, reversible phosphorylation of tau appears central to a measured program of neuronal preservation, working as a “master switch” regulating synaptic gain and maintaining and protecting neuronal networks (see Arendt and Bullmann, 2013; Bakota et al., 2017; Dave et al., 2012). From an adaptive point of view, maintaining neuroplasticity through torpor is critical to survival as it underlies useful learning such as environmental geography, dangers, water sources and food hoards. Hibernators exhibit remarkable synaptic flexibility (Horowitz and Horwitz, 2019). During torpor, tau is highly hyperphosphorylated, microtubules disintegrate, synapses retract and spine density decreases. Generally, tangles do not form in the brains of hibernating animals, though studies in aged bears find the presence of NFTs (Cork et al., 1988) even though bears are not strictly considered hibernators. Upon arousal, these changes rapidly reverse restoring the brain its pre-torpor state. The specific purpose of these changes in the phosphorylation state of tau is a matter of ongoing study but accumulation of pTau appears to prevent neurons from losing too many synapses by stabilizing the cytoskeleton (Arendt et al., 2003).

Hibernation may hold other clues to understanding the etiology of AD. Recovery of synaptic plasticity following hibernation depends on the coldshock protein RNA binding motif protein 3 (RBM3). This RNA-binding protein is upregulated during hypothermia and low oxygen tension and exhibits cell protective effects (Chip et al., 2011; Logan and Storey, 2020; Rosenthal et al., 2017; Zhu et al., 2016). RBM3 also regulates adult hippocampal neurogenesis in response to hypoxic ischemia (Yan et al., 2019; Zhu et al., 2019). Hypothermia protects against AD-like deficits such as tau hyperphosphorylation and learning deficits resulting from traumatic brain injury in an RBM3-dependent manner (Liu et al., 2020). Synaptic loss caused by cooling in a mouse AD model is coincident with reduced capacity to upregulate RBM3 and exacerbated by knockdown of RBM3 (Peretti et al., 2015).

16.3. Mis-sorting of tau

An aspect of tau that has gathered particular interest is so-called “mis-sorting” of tau to dendritic spines. This event, which is generally associated with synaptic dysfunction and neurodegeneration (Cochran et al., 2014; Guerrero-Munoz et al., 2015; Ittner and Ittner, 2018; Teravskis et al., 2020) appears to be driven at least partially by A β (Zempel et al., 2013; Zempel and Mandelkow, 2012). Dendritic spines are the main postsynaptic locus of structural and functional plasticity and the physiological role of tau in

learning, memory and synaptic plasticity is becoming increasingly recognized (Biundo et al., 2018). For instance, though there is some inconsistency in reports (see Ittner and Ittner, 2018), several studies show animals lacking tau exhibit deficits in LTD particularly. Neuronal excitation increases tau expression in somatodendritic compartments (Kobayashi et al., 2019) and tau is released into the extracellular space, which is instrumental in inter-neuronal spread (Pooler et al., 2013; Wu et al., 2016; Yamada et al., 2014). Though generally considered axonal proteins, microtubules are also found in dendritic spines and tau binding to microtubules may be involved in regulating structural and functional plasticity (see Dent, 2017; Penazzi et al., 2016).

Other than microtubules, tau has many known interaction partners, many of which have roles associated with synaptic plasticity. These include actin, ApoE, calcineurin, GSK3 β , Fyn, calmodulin and protein phosphatase 2A. Tau also interacts with HSP70 and HSP90 (see Ittner and Ittner, 2018). Tau can also undergo post-translational modifications other than phosphorylation that modulate interactions with other molecules. For instance, tau phosphorylation regulates protein interacting with PRKCA 1 (PICK1) binding to AMPAR GluA2 subunits leading to their internalization at the PSD, enhancing LTD (Regan et al., 2015). Acetylation of tau reduces the post-synaptic protein KIBRA (WW and C2 domain containing 1), disrupting AMPAR insertion and impairing LTP (Tracy et al., 2016). KIBRA is itself an intriguing adaptor protein associated with STC and long-term memory (see Schneider et al., 2010). Polymorphisms in the KIBRA gene associate with episodic and working memory (Milnik et al., 2012) and cognitive flexibility (Zhang et al., 2009) in healthy individuals and LOAD (Corneveaux et al., 2010; Rodriguez-Rodriguez et al., 2009), see (Schneider et al., 2010). KIBRA also protects against A β -induced apoptosis (Song et al., 2019a). Abnormal acetylation of tau found in AD brains disrupts synaptic plasticity by reducing KIBRA (Tracy et al., 2016). Interestingly, recent studies suggest KIBRA controls exosome secretion (Song et al., 2019b) thus implicating it in trans-synaptic spread of aggregating proteins (see section 17) which may have network-wide consequences on plasticity.

Evidence that accumulation of hyperphosphorylated tau is associated with neurodegeneration is virtually indisputable. (see Dolan and Johnson, 2010; Spires-Jones and Hyman, 2014). However, whether A β per se drives A β -induced tau *pathology* is contentious (Avila et al., 2004; Bloom, 2014; Guerrero-Munoz et al., 2015; Guo et al., 2017; Iqbal et al., 2016; Iqbal et al., 2010; Ittner and Ittner, 2018; Jadhav et al., 2015; Mandelkow and Mandelkow, 2012; Regan et al., 2017; Spires-Jones and Hyman, 2014; Wang and Mandelkow, 2016). Some have argued that other APP-derived fragments are responsible (Kametani and Hasegawa, 2018) or that tau pathology in AD can occur independent of A β (van der Kant et al., 2020). That pTau builds up in some tauopathies without frank changes in A β deposition certainly indicates that buildup of pTau to possibly toxic levels *can* occur independent of A β pathology but may not necessarily excuse A β of a permissive role. Furthermore, as mutations in the tau gene, MAPT, associate with these diseases strongly implicates alterations in tau metabolism as causes. Many kinases are implicated in in vivo tau phosphorylation many of which have known relationships with cellular networks controlling adult neurogenesis, long-term plasticity or STC. These include cyclin dependent kinase 5 (CDK5), PKA, PKC, Pyk2, GSK3 β and Fyn (Li and Gotz, 2018; see Martin et al., 2013). Some of these are controlled by G-protein coupled receptor signaling cascades (Chidambaram and Chinnathambi, 2020) or implicated in synaptic scaling or STC (Hernandez et al., 2016; Park et al., 2014; Seeburg et al., 2008; Sheng et al., 2016; Yagishita et al., 2015).

16.4. Hyperphosphorylation of tau

For the most part, phosphorylation of tau, particularly “hyperphosphorylation” and consequent aggregation of tau is considered a pathological event (Alonso et al., 2018; Iqbal et al., 2016). Phosphorylation of tau decreases its affinity for microtubules and thus hyperphosphorylation causes

cytoskeletal destabilization (see for example Alonso et al., 2018; Mieltska-Porowska et al., 2014; Tenreiro et al., 2014) causing synaptic collapse. However, whether the buildup of NFTs actually drives neurodegeneration is questionable (Cowan and Mudher, 2013). Consequently, highly phosphorylated soluble tau species are believed to be pathological, though even this view has been questioned (Castellani et al., 2008), and large tau aggregates may be protective by sequestering pTau (see Congdon and Duff, 2008; Cowan and Mudher, 2013; Iqbal et al., 2010; Shiarli et al., 2006). Also, like A β , tau serves beneficial functions to regulate neuronal excitation (see Kent et al., 2020). Either way, it is easy to imagine how a protein that plays a central role in maintaining cellular physical structure could take a role in neuronal outgrowth/retraction and structural plasticity (see Brandt and Bakota, 2017; Regan et al., 2017).

Indeed, regulation of tau dynamics could be integral to the STC process, acting particularly to prevent overexcitation or scaling down in post-synaptic neurons. Synaptic activity translocates tau into the post-synaptic compartment, as does exposure to oA β ₄₂ though curiously oA β ₄₂ blocks the activity-dependent translocation of tau (Frandsen et al., 2014). Tau translocation likely makes it available to interact with plasticity machinery such as glutamate receptors (Hoover et al., 2010; Pallas-Bazarra et al., 2019), Fyn (Larson et al., 2012; Lau et al., 2016; Li and Gotz, 2017; Roberson et al., 2011), GSK3 β (Hanger and Noble, 2011; Llorens-Martin et al., 2014; Tatebayashi et al., 2004), calmodulin (Barreda and Avila, 2011; O'Day et al., 2015; Yu et al., 2008a), calcineurin (Yin et al., 2016; Yu et al., 2008a), actin (Cabrales Fontela et al., 2017; Fulga et al., 2007; Yu and Rasenick, 2006), BDNF (Chen et al., 2012) and 14-3-3 scaffolding proteins (Chen et al., 2019) to name a few. It may also impact related processes such as adult neurogenesis (Fuster-Matanzo et al., 2012; Joseph et al., 2017). For instance, the degree of tau phosphorylation may reduce association with PSD-95 complexes leading to reduced NMDA-mediated excitability thereby preventing post-synaptic overexcitation (see Ittner and Ittner, 2018). Buildup of tau in neurons inactivates the late phase LTP protein CREB via calcineurin (Yin et al., 2016). Excessive levels of pTau may initiate a positive feedback loop leading to further phosphorylation of tau (Wei et al., 2018). Though knockout of tau generally has no effect on spatial memory (Ke, 2012 #1002) age-dependent short-term memory deficits have been reported (Biundo et al., 2018) and the prevailing view is that tau contributes to plasticity events; a process that turns awry and toxic in tauopathies (Biundo et al., 2018; Koller and Chakrabarty, 2020). There are several other mechanisms by which tau could impact synaptic plasticity (see Sotiropoulos et al., 2017) but particularly interesting are those that might occur under the direction of A β . As introduced above, Fyn-mediated control of NMDAR and PSD-95 interactions is required for A β toxicity which in turn depends on dendritic tau (Ittner et al., 2010).

Tau is also found in pre-synaptic terminals where in pathogenic forms it induces clustering of synaptic vesicles via actin (Zhou et al., 2017) and restricts their mobilization via the transmembrane vesicle protein synaptogyrin-3 (McInnes et al., 2018). Presynaptic tau oligomers also interfere with the action potential wave form and disorder synaptic transmission and plasticity (Hill et al., 2019a) as well as total tau downregulating transcription of genes involved in synaptic function (Pickett et al., 2019). Synaptic transmission is impaired in both pro-aggregant tau and tau-knockout mice coinciding with loss of synaptic vesicles (Decker et al., 2015). Accumulation of tau in synaptic compartments is controlled by bridging integrator 1 (BIN1) – the second highest AD risk gene (Glennon et al., 2020) – which also promotes extracellular pTau spreading (Crotti et al., 2019). Together these studies suggest tau in the presynaptic area could suppress afferent input, functioning to prevent interference with already established plasticity.

16.5. Tau as a register of established long-term plasticity

Observations such of these set the scene for tau itself potentially controlling long-term synaptic plasticity. Remarkably, it is still unclear if phosphorylation of tau drives pathology or is a protective response to pathology (Bretteville and Planel, 2008; Castellani et al., 2008; Congdon and Duff, 2008; Gotz et al., 2008). Or, is even directly involved in either despite the view tau phosphorylation causes dissociation from microtubules causing synaptic collapse (see Castellani et al., 2008; Tenreiro et al., 2014). Additionally, it is questionable that tau phosphorylation instigates formation into fibrils (see Tenreiro et al., 2014). For instance, pseudo-phosphorylation of tau decreases its rate of *association* with microtubules *without* impacting its *dissociation* rate. Thus, tau phosphorylation may prevent binding to filaments (and interacting with other partners) to lock cells into their current state of structural plasticity, rather than causing detachment and destabilizing structure (see Brandt and Bakota, 2017; Niewidok et al., 2016). Recent studies show that via PRPC soluble tau aggregates impair A β -facilitated LTD, block A β -mediated inhibition of LTP and increase the induction threshold for LTD (Ondrejcek et al., 2019). Interestingly these studies found that tau-mediated inhibition of LTD is independent of mGluR5 but depends on GluN2B subunits. LTD-inducing stimulation protocols enhance tau oligomerization in an age-dependent fashion (Kimura et al., 2017) and tau phosphorylation is necessary for induction of LTD (Kimura et al., 2014b; Regan et al., 2015).

These studies suggest that like A β_{42} aggregation, tau phosphorylation and aggregation may guard against changes in excitability and act out a program of preservation. Indeed, this notion is not novel. Referring to the antioxidant capacity of phosphorylated tau, Castellani and colleagues suggest that “the phosphorylated tau in AD is a *response* to the underlying pathophysiology and functions as an *adaptive phenomenon*” (my italics, Castellani et al., 2008). As Arendt and colleagues put it in reference to hibernation, hyperphosphorylation of tau may act to stabilize the cytoskeleton in an act “to ‘freeze’ the dynamic structure during a ‘*vita minima*’” (Arendt et al., 2003). Here, in hibernation, aggregated pTau may act as a stable intracellular non-volatile register resistant to changes in the metabolic environment. In this role, pTau may serve to protect neurons while simultaneously embodying an inventory, or image, of patterns of established neuronal connectivity so that experience-dependent plasticity established outside of torpor can be rapidly restored on waking. This may involve rapid cytoskeletal regeneration/stabilization, regulation of transport along microtubules or any number of other actions performed by tau’s interaction partners. That phosphorylation of tau also occurs in response to insults such as hypoxia, low glucose availability and physical trauma would be concordant with the same role – to maintain an image of established patterns of plasticity so that they can be restored in more favorable conditions. Notably, on waking from torpor, pTau levels rapidly decrease, presumably as metabolic state returns to normal and synaptic connectivity is rapidly restored to its usual means of maintenance. If so, tau must be able to play very active and direct roles in directing the molecular circuitry responsible for the creating and maintaining synaptic potentiation.

Why might pTau accumulate in AD? The answer may lie in the cellular distress experienced in memory circuits as they become overloaded. Like hibernation, buildup of pTau may constitute a battening-down of the hatches, a system-wide taking stock of established neuroplasticity to ride out encroaching conditions adverse to cell survival. This response may be well-intended, but simply goes too far. Several of the “pathological” effects of tau and pTau such as mis-sorting, spine loss and nuclear effects may be part of this preparatory response; a response that may constitute a mothballing of established plasticity into a form that retains its essence for re-elaboration once conditions improve. In the case of AD, this response is indeed downstream of increasing A β burden even if it was not the intended function of A β . Interestingly, recent imaging studies in humans show that in the presence of A β , high levels of aggregated tau associate with hypometabolism (Adams et al., 2019) lending support for this hypothesis and the notion that hyperphosphorylation and aggregation of tau reflect cells in distress. As such, and as

others have argued A β is not the actual neurotoxic agent. Even pTau may not be before reaching a specific level. Rather pTau and NFTs are insurance against the barrage of attempts to recruit cells into a system already at its maximum capacity. Consequently, NFT deposition better reflects neuronal death because even if it is not the neurotoxic “bullet”, it is a last stand action taken before cell death. That said, the relationship between A β and pTau is likely to be far more complicated than a simple linear connection. For instance, ApoE is among the many interaction partners of pTau (Drummond et al., 2020). The ApoE ϵ 4 allele exacerbates tau-induced pathologies independent of A β (Shi et al., 2017) and is associated with early age of onset in frontotemporal dementia (FTD) associated with MAPT mutations or FTLD-tau pathology, independent of A β (Koriath, 2019 #909). Additionally, recent human imaging studies suggest that the ϵ 4 allele modulates aggregated tau associations with memory independently of A β (Weigand et al., 2021).

A highly pertinent question is how reversible are these effects, or as Sotiropoulos and colleagues put it, where is the “point of no return” at which tau actions transition from a positive neuroplastic effect to a pathological effect? (Sotiropoulos et al., 2017). That hibernators can undergo repeated cycles of accumulating and dissipating large amounts of pTau encourages one to think that the system is dynamic and reversible. However, reversing accumulation of pTau away from neurotoxic levels is most obviously achieved by removing whatever insult triggered it in the first place, as is the case in hibernators (though hibernators do not exhibit large NFTs). This is not to say that slowing the process could not protect against disintegration of memory circuits, but this depends on to what extent pTau per se is neurotoxic.

16.6. *Tauopathies*

For reasons of scope and space I do not wish to speculate extensively on the etiology of tauopathies outside of AD. Nonetheless, given the discussion of the relationship between A β and tau, some comment is germane. Particularly, what causes deposition of NFTs and neurodegeneration in other tauopathies? Could this too be due to saturation of memory circuits? FTLD-taus, such as Pick’s disease, are classified based on the presence of tau-positive inclusions called Pick-bodies. Around 5 to 20% of FTLD-tau cases are associated with mutations in MAPT (Forrest et al., 2019; Pottier et al., 2016). Thus, mutations in MAPT cause FTLD-tau, but most cases of FTLD-tau are not associated with mutations in MAPT, though when mutations are evident, they appear to associate more with particular subtypes (Forrest et al., 2019). Importantly, FTLD-tau may help illuminate A β -independent functions of tau particularly as mutations in MAPT are not associated with AD. Remarkably, the amount of insoluble tau deposits in FTLD does not associate with the presence or type of MAPT mutation calling into question the notion that aggregation of tau directly drives the disease (Shiarli et al., 2006). Though there are a few overlaps in the symptomology of AD and FTLD caused by MAPT mutations particularly loss of episodic memory (Ghetti et al., 2015; Pottier et al., 2016), generally these two disorders present quite differently. Behavioral disinhibition, speech impairments and bradykinesia and a range of other distinguishing features are common in FTLD-taus depending on the specific variant (Young et al., 2018). This fact, and that FTLD-taus are mostly sporadic, questions if tau aggregation in FTLD-tau is a response to environmental factors, particularly localized insults. For instance, traumatic brain injury such as that found in combat veterans, American football players and boxers is associated with focal deposition of tau aggregates and neurodegeneration (Katsumoto et al., 2019). Extending the hypothesis above, this deposition may reflect registering and protection of established neuroplasticity as the brain attempts repair. Inflammation as a result hepatitis virus infection or administration of the endotoxin lipopolysaccharide exacerbates tau pathology in AD model mice (Sy et al., 2011) suggesting a similar role.

If tau deposition in FTLD-taus is a response to local insults then what specifically is this a response to, and what renders them localized? Unfortunately, relatively little is known of the risk factors for FTLD-taus specifically though risk factors for FTD (a subgroup of all FTLDs) are better understood. Aside from traumatic brain injury, risk factors for FTD include diabetes and autoimmune disease (Rasmussen et al., 2018). Interestingly, one study finds, opposite to that of AD, education is a negative risk factor (Borroni et al., 2008). Only one of these risk factors – head injury – might provide a ready explanation for localized insult though inter-neuronal spread of tau forms may mask the origin of insults.

17. Prion-like spread of misfolding proteins

In what might prove to be a major milestone in understanding the etiology of dementia is the discovery that many aggregating proteins are (1) able to induce aggregation of other like proteins, a process known as “seeding”, (2) induce aggregation of other very different proteins in a process called “cross-seeding”, and (3) released on neuronal activity and travel through neuronal networks. This process is called “prion-like spread”. Known proteins able to do this include A β , tau, α -syn, PRPC, SOD1 and Huntingtin; a list that is likely to grow (see Brundin et al., 2010; Goedert et al., 2010; Victoria and Zurzolo, 2017). Whether prion-like spread directly relates to aggregation ability is unclear but may be a common property. For instance, the PRP Arc undergoes oligomerization and is released from neurons where it is taken up by target cells and undergoes activity-dependent translation. Interestingly, the Arc sequence stems from a vertebrate lineage of retrotransposons that share a common ancestry with retroviruses (Ashley et al., 2018; Pastuzyn et al., 2018). Arc oligomerization is guided by CAMKII, which impacts its ability to control mGluR-dependent LTD (Zhang et al., 2019a).

The mechanisms by which misfolded proteins pass from cell to cell is not fully elucidated and may differ from protein to protein. Binding to synaptic vesicles, tunneling nanotubes, phagocytosis and exocytosis of exosomes are among the possibilities (see Victoria and Zurzolo, 2017). That misfolded proteins can pass between cells has naturally attracted great interest as it may explain how deposition and neurodegeneration occur in characteristic spatiotemporal patterns (see Brundin et al., 2010; Goedert et al., 2010; Marciniuk et al., 2013).

The central hypothesis presented here is that aggregating proteins mark and protect established changes in synaptic plasticity. Could transmission of aggregating proteins through neuronal networks be elemental to network level formation and maintenance of memories? As introduced above, a striking feature of pTau is that its accumulation precedes that of A β , accumulating first in isodendritic cells synthesizing neuromodulators, particularly LC NE neurons as early as childhood. Thereon pTau accumulates in the transentorhinal and entorhinal regions, then hippocampal and neocortical association areas, before finally appearing also in neocortical areas (**Fig. 4**). Here, it particularly impacts highly interconnected glutamatergic projection neurons while little impacting GABAergic interneurons (see Arnsten et al., 2021).

Isodendritic neuromodulators such as NE and dopamine are major governors of learning. This leads one to speculate if additional to aminergic modulation do isodendritic cells also distribute tau forms to learning circuits, and if so, does this relate to changes in synaptic plasticity and memory? Evidence supports a role of tau in limiting neuronal excitability in response to changes in plasticity (see section 16.4). Could this effect be long lasting and due to trans-synaptic transmission of tau? One possibility is that actin mediates tau effects. Actin dynamics are heavily implicated in structural neuroplasticity and synaptic tagging, possibly interacting with other PRPs such as Arc that cause changes in spine

morphology and stabilization (see Basu and Lamprecht, 2018; Pinho et al., 2020). Differential modulation of actin depolymerization/polymerization differentially affects induction or maintenance of LTD in a process mimicking the setting of a synaptic tag, which may act through CaMKII (Szabo et al., 2016). Several studies show tau associates with cytoskeletal dynamics through reorganization of actin (Biswas and Kalil, 2018; Elie et al., 2015; He et al., 2009; Sharma et al., 2007), but see (Roger et al., 2004) and modelling studies suggest actin may trigger aggregation of CPEB3 to modulate long term memory (Gu et al., 2020).

Studies such as these allow one to envisage that transmission of tau into memory circuits from isodendritic cells could contribute to STC in addition to imaging established plasticity. **Figure 5** presents a rudimentary scheme of how this might occur. Here, NE is shown as an example of isodendritic modulation and tau delivery, though other isodendritic modulators such as Ach and serotonin may exhibit a similar role. That hyper-phosphorylated tau appears early in isodendritic neurons may reflect their existence as sources of tau/pTau seeds to the brain, rising in these cells as a response to engramic circuits become saturated and possibly because presynaptic release suppressed. As pTau appears early in the transentorhinal cortex, the major gateway between the hippocampal formation and neocortex, one of tau's early roles may be to inventory memories as they are transposed from the hippocampus into the neocortex under the guidance of the hippocampal indexing system (**Fig. 5**). Thereon, tau/pTau may proceed from hippocampal to neocortical areas aiding in STC and/or registering areas of established neuroplasticity as the threat of overload increases. Supporting this notion, pTau seeding from entorhinal areas occurs earlier than from the LC (Kaufman et al., 2018). As A β accumulates in the neocortex due to memory overload, tau is unable to permeate into neocortical circuits consequently accumulating in the hippocampus and entorhinal cortex. Thus, a schema such as this could explain why aggregates of A β and pTau appear in approximately opposite directions in AD (**Fig. 5**).

18. Ach

Norepinephrinergic transmission signals states of novelty, arousal and vigilance to learning circuits giving them permission to learn. In contrast, Ach modulates the memory encoding process (see Haam and Yakel, 2017; Hasselmo, 2006; Teles-Grilo Ruivo and Mellor, 2013). Degeneration of mediobasal cholinergic neurons occurs early in AD providing evidence to one of the oldest theories of AD etiology - the cholinergic hypothesis (see Contestabile, 2011; Ferreira-Vieira et al., 2016; Francis et al., 1999). In support of this hypothesis, of the few drugs approved for treating cognitive deficits in AD, most act by boosting Ach tone. Unfortunately, the long-term efficacy of these drugs is questionable and none of them reverse the course of the disease. Why cholinergic neurons particularly are so vulnerable to degeneration in AD has been a long-standing question. One possibility is that like NE neurons, degeneration of Ach neurons reflects a compensatory response to prevent over-activation of saturated learning circuits. A β modulates cholinergic activity under physiological conditions and in physiological A β concentration ranges. These effects include modulating choline acetyl transferase activity (Kumar et al., 2018), decreasing choline uptake and modulating Ach release (see Kar et al., 2004). These actions may reflect the suppression of Ach learning inputs as A β accumulates coincident with temporary or permanent changes in neuroplasticity. The interplay between cholinergic signaling, neuroplasticity, misfolding proteins and neurodegeneration has been an area of intense research (see Buckingham et al., 2009; Lombardo and Maskos, 2015; Oddo and LaFerla, 2006; Schliebs, 2005; Yan and Feng, 2004). Much of this interest has understandably focused on α_7 NicRs given their central role in learning. A β binds to α_7 NicRs, M1 muscarinic and M3 muscarinic receptors, but does so to α_7 NicRs with unusually high affinity. As is a common theme, the outcome of A β binding to α_7 NicRs can range from possible beneficial

to negative effects, inducing neuronal death on one the hand but neuroprotection on the other (Buckingham et al., 2009; Farhat and Ahmed, 2017; Lasala et al., 2019).

The p75 neurotrophin receptor P75NTR may play a particularly important role in A β -cholinergic signaling interactions. P75NTR is expressed particularly in basal cholinergic neurons (Barker, 1998). A β binds to P75NTR to induce cell death (Knowles et al., 2009; Patnaik et al., 2020; Yaar et al., 1997). On the other hand, the ectodomain of P75NTR may be neuroprotective against A β (Yao et al., 2015) and sAPP α promotes neurite outgrowth by binding via P75NTR (Hasebe et al., 2013). Interestingly, P75NTR promotes A β production but coincidentally counters A β aggregation suggesting an action to increase A β turnover (Wang et al., 2011). This action may be related to P75NTR activation directing APP processing towards amyloidogenic processing via an interaction with BACE1 (Saadipour et al., 2018). P75NTR activation also promotes oA β ₄₂-induced hyperphosphorylation of tau (Shen et al., 2019) and loss of dendritic spines (Patnaik et al., 2020). These studies not only identify a discreet mechanism controlling differential processing of APP – a mechanism that may prove central to understanding AD – but also suggest cholinergic learning inputs may purposefully increase free A β ₄₂ levels. Ach also modulates plasticity via the PRP BDNF (Maurer and Williams, 2017) and it is noteworthy that P75NTR is a receptor for soluble BDNF where it acts to dampen synaptic plasticity (Sakuragi et al., 2013).

Altogether, the interface between cholinergic signaling and memory formation may be important to AD progression. Boosting Ach tone and activating nicotinic receptors can have pro-cognitive effects. This not only explains why nicotine itself improves concentration and learning, but why enhancing cholinergic transmission slows progression of cognitive decline in AD. That this effect is limited may reflect the limited ability of “overclocking” Ach tone to wring out the remnants of available mnemonic capacity.

19. Adult neurogenesis

Adult neurogenesis in the brain may be important to generating and maintaining long-term memories (Mu and Gage, 2011; Toda et al., 2019) but see (Lipp and Bonfanti, 2016) and others hypothesize a function in aging and AD (e.g. Dard et al., 2019; Kirschen and Ge, 2019; Llorens-Martin, 2018; Nehls, 2016; Teixeira et al., 2018). A perplexing question is why does neurogenesis continue throughout life when relative to all the neurons serving memory, adult born neurons are a very minor fraction? Put another way, why does the brain not just produce more neurons before birth? Or, reduce some of the great neuronal loss that occurs postnatally? What contribution could such a small number of new cells make to memories acquired over a whole lifetime?

The answers may lie in a role of neurogenesis in memory allocation. Adult neurogenesis occurs primarily in the subgranular zone of the hippocampus (Toda et al., 2019), an area critical to pattern separation - the process by which patterns of neuronal activity representing similar experiences are separated to prepare them for learning and storage. Without pattern separation newly experienced information could not be distinguished from and interfering similar previously stored information, causing confusion (Cayco-Gajic and Silver, 2019; though see Quian Quiroga, 2020). Activities that introduce learnable experiences, such as novelty, enriched environments and exercise all stimulate hippocampal neurogenesis (Kempermann, 2019; Ming and Song, 2011; Toda et al., 2019; van Dijk et al., 2016), whereas stress and sleep-deprivation have the opposite effect (Meerlo et al., 2009; Ming and Song, 2011). By recruiting freshly born cells, the hippocampus may ensure accurate and efficient pattern separation (Toda et al., 2019) guaranteed against interference from already established memories

(Sahay et al., 2011). As Drew *et al* note, each adult born granule cell may be viewed as a “blank canvas” (Drew et al., 2013). Such a function may not even require a large number of new cells. Just a few cells could constitute a linchpin to this process (Sahay et al., 2011). The vast majority of adult born granule cells are not permanently integrated into the hippocampus (Turnley et al., 2014). Thus, these cells may serve only a temporary function, acting as “scratch paper” on which pattern separation occurs before deliberate elimination following consolidation of short-term memories into neocortical circuits. In this manner adult born granule cells may act as a short-term plug in the system while new short-term memories are sorted for long-term storage or deletion. Once this process is completed, their removal may contribute to resetting of the hippocampus for new short-term learning. In line with this, studies suggest a role for adult neurogenesis in clearing memories from the hippocampus (Deisseroth et al., 2004; Feng et al., 2001) and limiting capacity to store short-term memories (Alam et al., 2018). For instance, decreasing neurogenesis stabilizes existing memories held in the hippocampus preventing encoding of new potentially conflicting memories (Epp et al., 2016) whereas increasing neurogenesis promotes forgetting (Akers et al., 2014). Particularly interesting to the current discussion are studies showing PSEN1 knockout mice exhibit impaired hippocampal neurogenesis and clearance of hippocampal memory (Feng et al., 2001). It is not possible to conclude that this effect is mediated specifically by decreased production of A β peptides as PSEN1 cleaves many proteins other than APP including notch, APLP1, APLP2, integrins and cadherins. However, this study hints at a role of A β in flushing the hippocampus of short-term memories via an action on neurogenesis. In support of this, intraventricular injection of anti-A β antibodies helps maintain object recognition memory apparently independent of memory consolidation (Lee et al., 2018c).

The phenomenon of childhood amnesia is an interesting and possibly relevant phenomenon. Children appear to lose all declarative memories formed before the age of three or four years while retaining memories such as motor skills and language. This phenomenon may reflect an adaptive process designed to clear the brain of early life plasticity deemed erroneous or of little use to adulthood in order to preserve memory capacity. Currently there is little data to support this notion, particularly regarding A β dynamics in very young children though relationships between ApoE genotype and development have been reported (see Wright et al., 2003). However, it is interesting to speculate that infantile memories are lost because of de-tagging A β -protected plasticity, or perhaps they were never A β ₄₂-tagged in the first place. Related, Josselyn and Frankland hypothesize infantile amnesia stems from the burst of hippocampal neurogenesis that occurs early in life whereby large numbers of newborn neurons oust out the established synaptic connectivity necessary for maintaining long-term memories (Akers et al., 2014; Josselyn and Frankland, 2012). Such a hypothesis is concordant with studies introduced above suggesting a role of new neurons in clearing hippocampal memories and forgetting. Relatively little is known about the role of A β in infant brains but given the intensity of childhood amnesia, study in this area may well unlock key understandings of the function of A β in aged humans.

Adult neurogenesis continues but progressively decreases until the end of life (Baptista and Andrade, 2018) but is markedly reduced in AD sufferers and generally reduced in AD model mice though findings are inconsistent (see Mu and Gage, 2011). The common molecular suspects implicated in AD such as ApoE, PSEN1 and APP-derived products present a mixed bag of negative and positive effects (Mu and Gage, 2011). This may reflect the complexity of APP-derived products and a multifaceted role in memory. Tau appears to be necessary for maturation of newborn granule neurons and their response to stimuli (Pallas-Bazarra et al., 2016). Whether or not impairments in adult neurogenesis observed in AD patients significantly contribute to cognitive deficits is unknown. Changes in neurogenesis appear at the early stages of AD before neuronal loss. This may reflect an early down regulation of hippocampal neurogenesis to protect long-term memory as it reaches maximum capacity. Alternatively, it may reflect

an attempt to hold memories in short-term hippocampal memory because they are unable to be deposited elsewhere. The inter-relationship between AD, sleep disturbances and neurogenesis may also reflect a system unable to distinguish and allocate recent memories to long-term storage. Given a role of adult neurogenesis in sustaining short term memories, continued research in this area is likely to be very informative to understanding AD.

20. What is the relationship between A β and tau?

There is no shortage of studies suggesting A β can induce phosphorylation and aggregation of tau and induce neurotoxicity and behavioral outcomes (see Bloom, 2014; Busche and Hyman, 2020; Pickett et al., 2019). It is the absoluteness and interdependence of A β and tau actions that is far from clear (Busche and Hyman, 2020; Puzzo et al., 2020). For instance, that the rare combined PS1/Christchurch ApoE3 mutation causes extensive A β plaque buildup absent of major tau buildup or neurodegeneration clearly shows that A β and tau pathology are dissociable (Arboleda-Velasquez et al., 2019). However, a more pertinent question is, what is the *physiological* relationship between A β and tau? Tau knockout mice show deficits in mnemonic processes (see section 16.4), but the effect of knockout, like that of APP is relatively benign. As is often with knockout studies, this may reflect compensatory changes in related molecules such as APLP2 and microtubule associated protein 1 (MAP1) (Ke et al., 2012; Weyer et al., 2014). Alternatively, the most telling phenotypes may not yet have been discovered due to the way experimental animals are housed or the behavioral paradigms being applied. That is, based on the current hypothesis, major phenotypes may not be uncovered unless animals are housed with lifelong and varied environmental stimulation capable of driving memory capacity to saturation and tested in behavioral paradigms that probe longer-term memory.

Relative to AD sufferers, FTLD -tau sufferers are typically viewed as exhibiting much fewer memory deficits (though see Hornberger and Piguet, 2012). This suggests tau acting alone plays only a minor role in the active process of establishing long-term neuroplasticity. Rather I propose that conversion of tau to pTau/NFTs primarily serves to register cells as having *undergone* changes in plasticity creating an image of established plasticity as backup against insults that could cause memory loss. *Inherently*, this process is related to A β deposition but only inasmuch that write-protecting and registering plasticity occur together, and the latter may only occur with encroaching saturation of memory circuits or other unfavorable conditions. This would explain why pTau buildup trails A β buildup.

Under normal circumstances this is a one-way process: registering (by pTau) only occurs if write-protected (by oA β_{42}) plasticity reaches critical levels. So, in this sense phosphorylation of tau *is downstream* of A β actions. But tau pathology *can* occur independent of A β buildup. Because, A β buildup is just one of many possible unfavorable conditions that promotes pTau buildup – the state that occurs in what is defined as AD. Molecularly, these two events may be connected as outlined above but other intracellular signaling cascades may yet be discovered. For instance, CDK5 is a kinase involved in tau phosphorylation and formation of tau aggregates (see Kimura et al., 2014a; Noble et al., 2003), the regulation of which is under control of A β (Hernandez et al., 2009; Town et al., 2002). Recent studies suggest that tau aggregates impair hippocampal LTP dependent on PRPC (Ondrejcek et al., 2018). This may suggest tau acts downstream of A β acting through PRPC though binding of aggregated tau directly to PRPC could be an equally possible explanation (Corbett et al., 2020). Furthermore, the ability of A β to hasten the spreading of pTau pathology depends on pTau binding to PRPC (Gomes et al., 2019). That tau itself is able to independently “impair” LTP suggests that under some circumstances, tau may work in concert, or join the fight so to speak, with A β to limit overexcitation.

A program of registering by pTau aggregation may only gather momentum as the threat of overload becomes more serious. The spatially distinct formation of NFTs and A β plaques in healthy aging suggests that at least initially these occur independent of each other (van der Kant et al., 2020). Possibly, only once does the threat of network collapse becomes significant does a relationship become more apparent and even then, the relationship may be more correlative than causal. On the other hand, correlative studies suggest A β deposition encourages tau pathology to proliferate through the cortex as AD takes hold (Price and Morris, 1999) though generally tau pathology precedes amyloid pathology (van der Kant et al., 2020). This again suggests pTau buildup may be a preparatory measure, which at least initially is protective (Castellani et al., 2008; Congdon and Duff, 2008; Cowan and Mudher, 2013). The question is: does pTau deal the actual deathblow? Based on the presence of pTau in hibernators, one might argue no. However, hibernators may not achieve toxic levels of pTau because the degree of pTau deposition is proportional to the level of saturation of memory circuits, which in the case of hibernators is below a critical level. Conceivably, as memory circuits saturate, pTau might impact A β deposition as an end stage attempt to firmly lockdown established plasticity entering into a vicious cycle as neuropathology sets in. In this sense, as Braak and colleagues have recently suggested, tau pathology may be viewed as the initiating factor in LOAD (Arnsten et al., 2021).

21. What causes neurotoxicity?

Before addressing this question, it may be worth asking what may seem like a heretical question, are forms of A β and tau *actually* neurotoxic? The amyloid cascade hypothesis has become so ingrained in our understanding of AD, the question almost seems ludicrous – to β abstists the term A β has almost become synonymous with the word toxic and causative (see Morris et al., 2014 for critical discussion; Morris et al., 2018). Nonetheless, it is undeniable that there is no shortage of studies showing A β_{42} *can* be toxic, especially in its oligomeric form, not just in the brain but across the whole body (see Carrillo-Mora et al., 2014; Guo et al., 2020; Kaye and Lasagna-Reeves, 2013; Reiss et al., 2018). But, does A β toxicity *cause* AD? The answer is surprisingly difficult to state definitively. One reason might be that many preclinical studies were conceived around the hypothesis that A β_{42} *is* neurotoxic. This is not to say that they are inherently biased, but the question may influence the means. Put another way, how many studies have been founded on the hypothesis that is *not* neurotoxic?! Additionally, many studies have used poorly defined forms of A β_{42} often applied at supraphysiological concentrations. Transgenic mice studies often use multiple human transgenes expressed at extremely high levels (Drummond and Wisniewski, 2017; Morris et al., 2014), which may only model EOAD at best. One could argue that even the questions being asked may not be particularly relevant. For instance, that A β_{42} blocks LTP has been reported numerous times but most studies have focused on hippocampal LTP. However, deficits in longer-term memory, which reside in neocortical areas are equally, and arguably the more troubling aspect of AD. Behavioral studies repeatedly show A β_{42} blocks formation of short- and long-term memories, but as discussed above, this type of memory is short in the context of a lifetime. Nonetheless, undoubtedly A β_{42} *can* be neurotoxic *and* exists in large amounts in AD brains. A β buildup certainly *appears* guilty and certainly needs to be accounted for in any explanation of AD. But figuratively speaking, is A β simply a passerby that picked up the smoking gun after the real perpetrator left the crime scene, or that the preclinical models developed have led to an entirely incorrect interpretation of the role of A β (see Krstic and Knuesel, 2013)? Based on the strong association between APP mutations and EOD, Hardy and De Strooper have reasoned not (Hardy and De Strooper, 2017).

Though the original amyloid cascade hypothesis (Hardy and Allsop, 1991; Hardy and Higgins, 1992; Selkoe, 1991) has come under increasing criticism (Amtul, 2016; Behl and Ziegler, 2017; Castellani and Smith, 2011; Castello et al., 2014; Chetelat, 2013; Kametani and Hasegawa, 2018; Krstic and Knuesel, 2013; Makin, 2018; Morris et al., 2014, 2018; Mullane and Williams, 2013; Pimplikar et al., 2010; Selkoe and Hardy, 2016; Skaper, 2012; Sorrentino et al., 2014; Tse and Herrup, 2017), the hypothesis still may have a lot of mileage in the current view. The framework described here may explain several observations that have troubled the hypothesis. Despite disappointing outcomes of lowering A β in clinical trials, evidence that A β accumulation beyond a certain point is problematic is difficult ignore. A β deposition starts in the neocortex in AD appearing then in hippocampal areas before accumulating in brainstem nuclei and caudal reticular nuclei including the LC. That the neocortex shows the earliest oA β_{42} deposition concurs with a hypothesized function of A β_{42} in protecting long-term memories. oA β_{42} naturally builds up as memories accrue and networks are recruited. This explains why so-called “pathological levels” of A β_{42} are found in cognitively normal individuals. These levels are only actually “pathological” if a critical point is reached and cells respond pathologically.

Perhaps then a more pertinent question is: why do only some cells respond pathologically? The answer, as disappointing as it may be, is that we may be unclear on exactly where the pathological threshold lies and why some cells are more resistant. Over a wide enough dose range, most biological molecular become toxic. For example, high concentrations of glutamate are excitotoxic and even water is neurotoxic if introduced into the brain at high enough levels! The threshold for A β toxicity may be far higher than we think but once crossed triggers a vicious cycle of neuronal hyperactivation (Stargardt et al., 2015) which itself may involve glutamate-driven hyperactivation (Zott et al., 2019). And if so, it is unsurprising that humans can surpass that threshold given that they live twice as long as they did just a few centuries ago. Additionally, depositories of aggregated proteins may exist to ensure that *functional* prions remain aggregated by pharmacodynamically swinging equilibration in their favor. In fact, amyloids by their nature are generally unreactive and inert and so large deposits may indeed not be toxic as the AD field is coming to appreciate (Goure et al., 2014; Morris et al., 2018; Yankner and Lu, 2009). It is also important to consider that the points at which A β induces toxicity are unlikely to overlap completely with those mediating physiological functions (**Fig. 3A**). For example, though it is clear that A β acting via PRPC can be neurotoxic (Purro et al., 2018; Smith and Strittmatter, 2017; Zhang et al., 2019b) some studies suggest that binding of oA β to PRPC may not necessarily have a toxic outcome (Mengel et al., 2019). Soluble forms of PRPC may inhibit its neurotoxicity, acting perhaps to mop up or buffer excessive oA β (Purro et al., 2018; Zhang et al., 2019b), suggesting that PRPC cleavage may be a natural mechanism for countering excessive amounts of A β .

It has long been clear that the spatiotemporal pattern of A β deposition maps poorly onto the progression of cognitive deficits (Morris et al., 2018). Deposition and aggregation of A β_{42} in neocortical circuits is likely to be under close directorship of hippocampal activity. Not only because the hippocampus temporarily stores these memories but also because the hippocampus may retain the cognitive map or index used for their allocation and retrieval (Goode et al., 2020; Teyler and Rudy, 2007; Wikenheiser and Schoenbaum, 2016). Here I suggest that it is because long-term memory circuits are saturated first that hippocampal memories cannot be consolidated into the neocortex, lingering in the hippocampus. This would explain why anterograde amnesia precedes retrograde amnesia in AD and why A β_{42} deposition appears first in the neocortex (**Fig. 4**). With time, A β_{42} accumulates in hippocampal areas as attempts to transpose memories into the neocortex become increasingly unsuccessful. Recent studies support this prediction as they suggest that tau pathology in the mediotemporal lobe functionally isolates it from the hippocampus in AD (Harrison et al., 2019). This would also explain why AD does not reach clinical recognition until A β_{42} starts to accumulate in the hippocampus. This is certainly not to say

A β ₄₂ does not have a hand in storing hippocampally-held memories stored over waking periods, which may last hours to days. Write-protection is needed here too. It is tempting to speculate that memories are transferred along hippocampal-neocortical projections *along with* A β ₄₂ in a prion-like spread. Thereon, A β ₄₂ oligomerizes to locally write-protect and direct the production of pTau (if memory saturation is being approached), which may be distributed from isodendritic neurons, providing the permission and material to construct the image of established plasticity. Though hugely speculative, if no appropriate opportunity for establishing a change in synaptic efficacy is available, the engram may percolate through memory networks along with A β ₄₂. Once the new information finds an appropriate storage point it is laid down and protected by A β ₄₂ aggregation. As such, new engrams permeate through already established networks of write-protected plasticity without them corrupting each other, possibly cross-referencing and comparing them as they go.

21.1. Are all A β -induced “neurotoxicities” “neurotoxic”?

With the above in mind, some of the apparent neurotoxicities associated with AD such as synaptic loss may be the result of deliberate reorganization of memory networks to increase their efficiency as memories accumulate. They may also serve to protect against potentially harmful attempts to recruit write-protected neurons into new engrams. For instance, dendritic spine loss is considered a negative process. However, A β -induced “dendritic simplification”, which depends on calcineurin (Wu et al., 2010) may be part of a program to eliminate unnecessary spines to optimize efficiency and/or deliberately disconnect neurons. Likewise, “aberrant” neuronal sprouting (Masliah et al., 1991; Phinney et al., 1999) may be a compensation in a system driven to its extreme. That spine elimination is mediated through calcineurin accords with a general theme of calcineurin in constraining LTP (Baumgartel and Mansuy, 2012). Calcineurin is associated with elimination of long-term memories (Lin et al., 2003; Sachser et al., 2016). It is possible that this function is intended to prevent storage of duplicate or conflicting memories or possibly to allow some memories to fade or be disconnected from others. Buildup of aggregating proteins may become toxic because they *reflect* a system that is overloaded and lacking the temporary space to organize or re-organize itself (akin to a swap file in computer terminology). That is, sensing this overload the brain mobilizes responses to increase its efficiency but ultimately the finite nature of the brain dictates its doom. For example, a long-recognized deficit in AD brains is overexcitation and network instability, believed to underly proneness to seizures in AD (Li and Selkoe, 2020; Palop and Mucke, 2010). In a highly influential study, working with hAPP_{FAD} mice, Mucke’s laboratory speculated that neuronal overexcitation results in the development of compensatory inhibitory mechanisms, which though well intended, end up constraining the “agility” of excitatory circuits underlying memory (Palop et al., 2007).

Perhaps most concerning to the amyloid cascade hypothesis is why attempts to mitigate the disease by targeting A β have met little success. In some cases, they have even worsened cognitive decline. At least two scenarios are possible. Decreasing endogenous A β ₄₂ levels is unlikely to impact already write-protected neurons unless free extracellular A β ₄₂ shifts to a point low enough to encourage disassembly or dissociation of oA β ₄₂ bound to cellular receptors. If A β fibrils and plaques play an active role in determining this threshold, then this must be taken into consideration before targeting them as it may cause memory loss. That said, there have been numerous experimental therapeutics reducing brain A β burdens or peripheral measures of A β ₄₂, sometimes massively, yet these have failed in clinical trial (Liu et al., 2019b; Panza et al., 2019a). There may be many reasons for this but a major one is that doses of these therapeutics required to achieve or even approach a reduction enough to impact A β ₄₂-write protection enters into the realm of significant off-target effects that bring their viability to an end (Mehta et al., 2017; Panza et al., 2019a). Furthermore, even if one is able to eliminate oA β ₄₂-mediated write-protection, the *initial* outcome would be *loss* of long-term and maybe even short-term memory,

which would manifest as cognitive worsening, at least in the short-term. This leads one to speculate on the instruments used in clinical trials. For instance, though the widely-used MMSE and ADAS-Cog scales assess long-term memories in the course of for example assessing naming and orientation (e.g., What is this? What is the month?), they do not assess very distant memories (e.g., Where were you born? What was your first car?), which might be very informative. Reducing endogenous A β_{42} levels may also block use of any remaining memory capacity, which again would manifest as cognitive worsening. In either case, reducing A β_{42} levels may halt disease progression though it may require sacrificing remaining potential for anterograde memory and exacerbating retrograde amnesia.

A seldom asked question is *why* nature has produced two distinct pathways of APP processing. BACE1 directs APP processing towards amyloidogenic processing. Yet, the vast majority of mutations associated with FAD are in γ -secretase in APP genes (see <https://www.alzforum.org/mutations>). Knockout of BACE1 impairs memory and prevents A β plaque buildup in APP model mice but has surprisingly mild effects generally though does alleviate impairments in APP model mice (Laird et al., 2005; Luo et al., 2003; Ohno et al., 2004). As has been pointed out by others, there is still much to learn about the processing of APP (Castro et al., 2019). Of what is already known, only a small part has been covered here. The reader is referred elsewhere for further information (Chen, 2015; Chow et al., 2010; Zhang et al., 2011). Though my focus has been on A β_{42} given its propensity to aggregate, the role of A β_{40} and its relative concentration (the A β_{40} :A β_{42} ratio) is attention worthy. For instance, factors such as ApoE ϵ 4 status (Fryer et al., 2005), angiotensin (Zhu et al., 2011) and interactions between synaptotagmin and PSEN1 (Zoltowska et al., 2017) all govern the ratio. Recent studies show the ratio correlates very highly with tau pathology in human neuronal cell cultures (Kwak et al., 2020). Understanding the outcome of this ratio becomes even more important considering studies suggesting A β_{40} prevents amyloid deposition (Kim et al., 2007; Kwak et al., 2020) and competes for binding to A β aggregates (Jan et al., 2008). Even small differences in the ratio can impact neurotoxicity (Kuperstein et al., 2010).

22. Does A β cause AD?

As Morris and colleagues emphatically point out referring to A β pathology as being a *defining* characteristic of AD: “the current neuropathological diagnosis of AD dementia is in fact a diagnosis of a working hypothesis of disease aetiology” (Morris et al., 2018). Indeed, one could argue that the cards have been stacked against A β from the start. So, does A β cause AD? The short answer is a qualified yes – it most certainly is *instrumental* in the disease process. One need only look at the effect of administering oA β_{42} into healthy brains to see that this is the case. But, A β is neurotoxic only inasmuch that overaccumulation of A β_{42} through a natural physiological process triggers a neuropathological response. Here, saturation of oA β_{42} -protected memory circuits is the hypothesized cause of AD. A β_{42} write-protects plasticity and so A β could partially or wholly “cause” AD. Put colloquially, it was never the intention of A β_{42} accumulation to have such devastating consequences any more than hyperinsulinemia intends to threaten the life of type 2 diabetics. Indeed, any molecule that synaptically tags neurons might have the potential of becoming neurotoxic³.

³ Though it is beyond thorough discussion in the current article, there may be evidence that other aggregating proteins found in neurodegenerative diseases fit this bill. For instance, α -syn displays several remarkable resemblances with A β . Other than being a misfolding protein implicated in neurodegenerative disease it regulates synaptic plasticity (Burre, 2015; Cheng et al., 2011), it is found in areas of the brain exhibiting high degrees of plasticity (particularly the hippocampus and substantia nigra), shows prion-like spread (Clavaguera et al., 2020),

Does A β work alone? Whether A β_{42} *directly* instigates neuropathology is questionable and if it does, whether this is an extreme case of a natural process is even more unclear. A more reasonable view may be that cells initiate responses on detecting overaccumulation of A β that though well intended, end up being neuropathological. Responses that involve many players and processes, many of which have been discussed in the extensive literature but are not covered here.

AD is one of many dementias caused by neurodegeneration. That many of these dementias are coincident with accumulation of misfolding proteins is both striking and uncanny. Understandably, focus has been mostly placed on this coincidence viewed through the lens of pathology. However, the key to understanding the pathology may be found in viewing this coincidence through the lens of physiology. Other dementias may present similar pathological responses without overaccumulation of A β_{42} because as introduced above, A β_{42} overaccumulation is just one of many potential insults that prompts common downstream effects, such as tau phosphorylation. Indeed, it is becoming increasingly evident that dementias are nuanced phenomena. It may be safer and necessary to classify them into general categories for the purpose of diagnosis and treatment but their etiology lies in multidimensional spectra of pathological changes. If one looks into the brain of any aged individual, one finds buildup of a range of “pathological” misfolded proteins many of which may be serving important and beneficial functions. Only once they have passed a certain level do they become undesirable and problematic producing the stereotypical patterns of cognitive impairment that are classified into various dementias.

So, what specifically is AD? AD is not so much a disease, but a syndrome (see Fox, 1989 for discussion of the historical elevation of AD from senility to disease status). This statement is by no means intended to lessen the gravity of the condition. As others have pointed out (Arendt, 2001; Mesulam, 2000; Meyer et al., 1998), but contrast with (Morris, 1999) I submit that given enough time AD inevitably develops in any sentient individual that continues to be exposed to and internalize new information, or even simply generates new memorable memories through introspection. This relates to several important questions that have troubled the field for a long time. Firstly, back to the question, is AD caused by A β ? Here, one must be careful of not entering into a circular argument. The very definition of and diagnosis of AD is based on the presence of A β plaques and NFTs. Over the years these events have virtually transcended from being symptoms to being a cause, largely driven by the amyloid cascade hypothesis (see Morris et al., 2018 for discussion). As I have argued here, *overaccumulation* of A β prompts a neurotoxic process that damages memory – there is nothing radical about this statement. In this respect, the amyloid cascade hypothesis does have legs and one should be careful before abandoning it - we might be throwing the baby out with the bathwater. However, what we call AD may be better described as a syndrome of *A β -impaired* and (possibly) *NFT-impaired* cognitive function. To emphasize, the keywords here are “impaired” and “cognitive function”. This may or may not be accompanied by the “neuropathological” features A β plaques and NFTs, which currently define the disease (Jack et al., 2018). This syndrome can appear alone (call it AD), overlap with other dementias (which it often does) and be present to some degree in relatively “healthy” individuals (which is inevitable). Indeed, meta-analytic analyses of the relationship between A β burden and cognitive performance conclude a positive relationship even in cognitively “normal” individuals (Baker et al., 2017).

This leads to a second question: is AD on a continuum with “healthy aging” (see Swerdlow, 2011)? Many have argued no (Ghosh et al., 2011; Greicius et al., 2004; Morris, 1999; Nelson et al., 2011). However,

interacts with PRPC/mGluR5 (Ferreira et al., 2017; Rosener et al., 2020), interacts with actin (Bellani et al., 2010) and has been proposed as important to STC and maintaining lifelong memories (Clayton and George, 1999).

the answer may again relate as much to semantics and definitions as it does to scientific facts. Firstly, I contend that the main issue is *experience* not the passing of time – an important distinction. A more suitable term would be akin to “experiencing” as clumsy as the term is. Secondly, the word “healthy” in this context is really defined as not being *overtly* pathological in terms of being afflicted beyond some *reasonable* expectation; an expectation that may previously have been simply known as “senility” before it acquired the negative undertone it now holds. This has prompted definition (or cynically speaking, creation) of related conditions such as “age-related cognitive decline”, “mild-cognitive impairment”, “preclinical AD” and “prodromal AD”. But these are arguably different degrees of similar conditions that could depend on oversaturation of memory circuits. Some of these may be prelude fully blown AD. Others may take a different course, perhaps one where some other aggregating protein reaches toxic levels. Whether these conditions develop into AD depends on if overaccumulation of A β is driving the cognitive changes and whether or not this situation worsens or is rescued by some endogenous mechanism.

All of the above suggests that, as unpalatable as it may be, AD is as much a part of “healthy aging” as osteoarthritis or tooth decay is – both result from *using* organs for what they were *intended*. Defining AD as a syndrome characterized by a trifecta of A β plaques, NFTs and cognitive deficits is reasonable. And, defined as such, it would be accurate to say that AD is caused, at least in part, by *overaccumulation* of A β . But this has limits. A β accumulation does not inevitably mean cognitive deficits, only *overaccumulation* of A β does. And this is not unique to AD. A β and tau accumulation *naturally* occurs through life because memories naturally increase through life. Only on reaching a threshold do they cause changes in cognition termed “deficits”, thus completing the trifecta called “AD”. This is not to say that AD as defined by the trifecta of A β plaques, NFTs and cognitive decline may only result from memory oversaturation. Certainly, this the most likely scenario in the case in sporadic forms. But, like many diseases, factors such as genetic mutations, unrelated disease processes and environmental factors could generate or exacerbate this trifecta. This is likely to be the case in familial forms and rare variants such as HIV-associated AD.

23. Could AD be caused by information overload?

Globally, the average life expectancy of humans has more than doubled in the last two centuries (Roser et al., 2013). Simultaneously, not only has the accumulated amount of human knowledge increased massively, but also have means for disseminating and storing information – the so-called “information age”. For instance, in 2010 Google estimated that more information was created every two days than had existed worldwide prior to 2003 (Peder Zane, 2015). Moreover, means of information dissemination such as television and the internet are increasingly information-rich compared to older media such as books and spoken-word radio. Opportunities for experiencing more sensory information such as by digital media, traveling, video games and schooling have also increased. Information is far more accessible than it has ever been, often being no further away than the smartphone in a pocket. As nations have become industrialized, individuals compete less for employment and survival based on physical prowess and practical skills but more on the basis of intellectual ability and knowledge. This has led more people into further education and employment involving assimilating and processing large amounts of information. At the same time, humans have more leisure time than ever as their ingenuity in tool construction alleviates them of the need to physically toil for survival. To avoid boredom, this leisure time is often filled with activities that too deliver large amounts of information such as watching television, playing video games, listening to music and browsing the internet. Even sleep patterns have changed. Prior to the industrial revolution, it was common to sleep in segments waking for several hours

and going about tasks and leisure activities in the middle of the night (Ekirch, 2005) thus allowing more frequent breaks.

Humans appeared on earth approximately two million years ago. Modern humans appeared around 200,000 years. The changes in life expectancy and lifestyle they have undergone in the last 200 years have occurred virtually instantly on this timeline. The success of modern humans owes much to their superior intellect and ability to acquire and communicate knowledge and wisdom from generation to generation. As human populations rise so has competition for resources leading humans to create incredible wonders of technology used not only to solve the complex problems that threaten their survival but also to commit horrific atrocities on each other and their environment. In general, one could reasonably argue that humankind has reached a point of their own making beyond which they are no longer adapted. In a sense, humans are victims of their own success “thinking themselves to death”. In the *Descent of Man*, Darwin acknowledged the “god-like intellect” of humans yet emphasized they cannot deny they carry the “indelible stamp of his lowly origin”. As Hamlet put it, “this quintessence of dust” despite it (oddly) following a statement of “how infinite in faculty” are the minds of man. That is, brains are finite in their abilities including their ability to store information. Though logic dictates this fact, the notion that the human brain could reach capacity is almost unfathomable to many, and even comical as exemplified in the *Far Side* cartoon of a student asking their teacher “May I be excused? My brain is full”. However, there may actually be a great deal of truth behind this joke. We have little difficulty accepting that short term memory is finite – many studies have studied this phenomenon, going back to Miller’s (Miller, 1956) magical number of seven plus or minus two (though see Macken et al., 2015). However, accepting that long-term memory is finite seems more unpalatable, especially to generations raised on the myth that they only use 10% of their brains. Interestingly, attempts to predict the memory limit of the human brain have been made; a limit predicted to be around several petabytes (see Namaziandost and Ziafar, 2020). To put this in context, the current version of all articles in Wikipedia can be compressed into about 20 gigabytes. The digital collections of the Library of Congress (the largest library in the world) is currently estimated to be around 3 petabytes. However, estimates on the storage capacity of the brain are generally derived from the number of neurons and synaptic connections it contains, much of which are not dedicated to declarative memory but rather to functions such as olfactory, visual and auditory memory, and implicit memories underlying processes such as motor skills and habit-based behaviors. Furthermore, information storage in brains is likely to be far more sophisticated than the binary storage methods of computers and so viewing memorable information simply as bytes is probably overly reductionist.

As one lives longer, one accumulates more experiences and information. Why has the brain not evolved a solution to overloading? It is as if evolution of the mnemonic capacity of brains outpaced needs until recently, perhaps because having spare capacity is an important safeguard against overloading. However, that need may have been abruptly met giving relatively little opportunity to evolve a natural solution. Solving this overloading problem has not been tackled as there has been little adaptive pressure to do so. One may even argue that there still is little pressure to do so. For instance, most dementias typically set in long after menopause at a time when child-rearing is complete (though knowledge and wisdom, which are important to the survival of the next generation, continue to accrue until the end of life).

23.1. The problem of forgetting

Why does the brain not simply avoid the issue by disposing of some memories, i.e., forgetting? Even anecdotal experience tells us that deliberate forgetting is difficult. Some memories may be forgotten spontaneously either by natural turnover in memory circuits or simply due to malfunction (Davis and

Zhong, 2017). In some cases, events and thoughts that appear forgotten may actually be due to them not being remembered in the first place. In other cases, though somewhat degraded, they require specific cues to recall them as interference by other memories blocks accurate recall. For example, one may find it difficult to recall a PIN number for an ATM card that has not been used for a year, yet presented several possibilities of which only one is correct, there is a strong likelihood that the correct one will be chosen. Anecdotal experiences such as these affirm the notion that we remember more than we are consciously aware of or that we can recall. This often leads to the metacognitive struggle of something being “on the tip of our tongue” knowing that we know something but not being able to recall it; a condition that likely underlies *lethologica* and *lethonomia*.

Certainly, memories can be *updated* through the process of reconsolidation (Lee, 2009) and some have argued that proper brain function must employ mechanisms for deliberate forgetting (Gravitz, 2019). However, the brain is presented a major problem: even if it could forget, what should it forget and on what basis (Gravitz, 2019)? The answer likely lies in the fact that the mind does not have the level of executive control to make this “choice” particularly as a means for deliberately freeing storage capacity. Take as an analogy the situation of a library that has reached storage capacity. In such a case, the librarian may judiciously choose to dispose of some little-read books to make way for newer books. However, the brain does not have this level of executive control because it is difficult to assess which memories are most valuable to the present or future. One might reason that consciousness should provide such an executive level function but as consciousness emerges from and is embroiled in lower or discrete brain functions, possessing the ability to directly alter underlying brain processes would inherently mean consciousness would have the ability to shape itself. Besides, in disposing of the little-read virology textbook the librarian unwittingly doomed all the library members to succumb to the viral epidemic that hit the next day.

Certainly, memories fade with time, or at least emotional reactions to them do, but it would be difficult to challenge the view that older people do not have more memories than younger people or that they have more problems accessing them. Consciously, selectively and deliberately forgetting information is difficult though evidence does exist for “motivated” or “conscious” forgetting (Anderson and Hanslmayr, 2014). This process may be directed at distressing memories such as those causing trauma, embarrassment or conflicting with a held world view, or to avoid conflict with new memories of a very similar nature. Interestingly, motivated forgetting may involve the Rho family GTPase RAC1 and center around actin dynamics (Davis and Zhong, 2017). Certainly, being able to consciously and selectively forget information would be a useful but dangerous skill and has formed the plot of many works of fiction. However, in reality motivated forgetting is generally very selective and probably impacts only a tiny fraction of memories though it is interesting to note that AD sufferers are impaired in their ability to actively forget (El Haj, 2016). Much of the information acquired by the brain is learned passively and is emotionally innocuous, giving little motive for it to be deliberately forgotten. The memories most readily recalled and resistant to forgetting are those formed in association with emotive events. It was their association with emotional response such as fear, pleasure and surprise that caused them to be stamped into memory circuits so firmly in the first place because these are memories of particularly important or salient events, which likely explains why psychiatric disorders such as PTSD, obsessive compulsive disorder and addiction are so difficult to treat. The problem may be compounded by the possibility that the more one tries to forget an event, the more one consciously recalls that event, causing the memory only to be strengthened.

23.2. What evidence supports a memory overload hypothesis?

The notion that AD could be caused by overload of memory circuits is not entirely new. In an article published nearly 20 years ago, Clarke presented a similar hypothesis reasoning that differential phosphorylation of tau embodies stored information (Clarke, 2000). Clarke reasoned that the large number of phosphorylation sites possessed by tau provides a digital encoding mechanism with up to 17 billion variations. Once all variations are exhausted, pTau forms NFTs driving neurodegeneration. Clarke did not elaborate specifically on how cells could recognize and distinguish 17 billion variations in tau phosphorylation, or for example how the many molecules of tau found in the same cell could be distinguished. Nor was an explanation of how this would manifest in neuroplasticity and circuit connectivity provided. Nonetheless, Clarke essentially proposed that pTau acts as a mnemonic tag. Additionally, Clarke proposed that A β acts as an anti-overload mechanism noting that A β initially promotes plasticity before switching to an inhibitory and ultimately a toxic role. Indeed, the notion that A β transitions from positive and beneficial mnemonic effects to neurotoxic effects is by no means novel - several others have made the same suggestion (Morley et al., 2019; Puzzo, 2019).

Around the same time as Clarke's article, Mesulam published his "plasticity-based theory of the pathogenesis of AD" (Mesulam, 2000). Noting the correlation between areas of high plasticity and deposition of A β and NFTs, his article made a number of remarkably relevant statements. Asking "Could the increased vulnerability of limbic areas to NFT formation be based on the increased neuroplasticity load they have to bear throughout the life span?" Mesulam went on to surmise "Ultimately, AD arises when the brain can no longer keep up with the work needed to repair itself or encode new experiences" and that "AD of old age may not be a disease at all, but the inevitable manifestation of a failure to keep up with the increasingly more burdensome work of plasticity". Additionally, Mesulam suggested that in areas of high plasticity tau phosphorylation and A β turnover initially act adaptively and independently to meet neuroplasticity needs – a concept similar to that presented here. Eventually, Mesulam proposed, such processes would "lead to chronically high and eventually unsustainable levels of plasticity-related cellular activity" following which such pro-AD factors transition to neurotoxic effects. Moreover, Mesulam made what proved a particularly prescient prediction, suggesting that attempts at reactive remodeling to counter increasing plasticity burden, NFTs would form and undergo a "horizontal" spread in inter-connected brain regions – interest in prion-like spread of tau forms was not to take off until a decade later (Goedert et al., 2010).

Is there any tangible *direct* evidence supporting the prediction that long-term memory overload causes AD? The short answer is no, or at least very little. Perhaps because studies attempting to deliberately overload memory in humans or experimental animals are practically non-existent. That said, very recent studies by De Risi *et al* suggest that week-long memory capacity in aged cognitively impaired mice is limited by an autophagic process that eliminates fibrils of A β and α -syn (De Risi et al., 2020). However, studies such as this are unusual, obliging one to look to correlative evidence. Aside from the risk of developing AD increasing with age and the notion held (by some) that all individuals will develop AD if they live long enough, epidemiological evidence may be supportive. As outlandish as it may sound, several studies show television viewing correlates with AD risk (Lindstrom et al., 2005) and mortality (Grace et al., 2017; McDonnell et al., 2016; Veerman et al., 2012). Though naturally these studies are difficult to interpret as time spent watching television is time not spent doing activities such as exercise – activities that themselves may be negative risk factors in their own right. If one supposes industrialization has brought concomitant increases in exposure to information rich experiences, one might look to comparing AD rates in industrialized versus non-industrialized countries. Comparing African Americans with Nigerians finds higher rates of AD in the former (Josefson, 2001). AD incidence is generally higher in North America and Europe than in developing countries (see Qiu et al., 2009).

However, again studies such as these are open to confounding variables such as diagnosis techniques, genetic diversity, differences in education level and lifestyle.

Perhaps if one turns to other animals one might find supportive evidence. Cognitive dysfunction appears in several domestic animals including dogs, cats and horses, showing much of the same pathology with AD (see Prpar Mihevc and Majdic, 2019). One might speculate that this is due to the unnatural extension of their lifespan through artificial breeding, shielding from predators and veterinary care while also experiencing more enriched lives provided by their human owners. Generally, wild-type mice are viewed as being less prone to developing AD-like pathologies though A β aggregates are found in brains of aged mice (Ahlemeyer et al., 2018; Geng et al., 2020). That neurodegenerative diseases generally do not spontaneously appear in laboratory rodents may reflect their particular genetic background and the conditions in which they are reared and housed, which amount to environmental deprivation. If this is the case, then more natural, stimulating and highly enriched living environments in which animals are housed over a lifetime will be key to producing more valid experimental models. As will be using more demanding cognitive tests, such as that employed by De Risi colleagues introduced above (De Risi et al., 2020).

Maintaining cognitive activity such as reading, puzzles and learning new hobbies appears to protect against dementia (<http://www.alzrisk.org>). These activities likely exercise and reinforce established plasticity through deliberate recall of information, acting as reminders without adding much new information. Though entirely speculative, these activities may also be necessary for reorganizing memory circuits to improve accessibility in processes akin to defragmenting a computer hard disk. They may also increase storage efficiency by compressing information; again, speculation but worthy of consideration. For adjustment and reorganization to occur, recall of memories must occur to render them labile and open for modification. Recent modelling studies suggest that just a few hypothetical protein synthesis inhibitor-resistant stabilizing molecules or complexes held in a reservoir could take on a write-protect role to determine consolidated synaptic plasticity and its opening up to reconsolidation (Kastner et al., 2016). oA β_{42} may fit this bill. Recent studies show that A β is required for stabilizing fear memories at the time of consolidation and protecting them against reconsolidation events (Finnie and Nader, 2020). This suggests that A β write-protection could be very strong, at least for amygdala-dependent emotionally-laden memories such as fear. However, studies of this kind are also few. One such finds that the 5xFAD AD model mice are unable to reconsolidate fear memories (Ohno, 2009). This might relate to the poor ability of AD sufferers to actively suppress memories (El Haj, 2016). If indeed A β does mark neurons as write-protected then understanding its function in reconsolidation is a worthy area of study, especially as one turns their attention to therapeutic strategies.

24. Counter-arguments and unanswered questions

The evidence presented here has largely argued the case for A β and pTau aggregation in maintaining and protecting memories. However, many questions remain. Some of these have been partially addressed above though undoubtedly the answers may be incomplete or unsatisfactory. Following is a list of some counter-arguments and questions:

Counter-arguments:

- If APP products are so important to protecting and maintaining long term plasticity then why were they not discovered and implicated in memory before receiving attention in AD?

- Given the close relationship between memory, intelligence and cognition, why are mutations in APP and APP processing genes not more common in mental retardation?
- Most evidence points to PRPC mediating toxic effects of $\text{oA}\beta_{42}$. What evidence points to physiologically beneficial effects in lifelong memory?
- If PRPC serves as a common receptor for aggregating proteins, why are mutations and polymorphisms in PRPC so rare in neurodegenerative diseases other than prion disease?
- Why are $\text{A}\beta_{42}$ levels reduced, not elevated, in the CSF of AD patients?
- How could the oligomerization state and size of $\text{A}\beta_{42}$ be detected with such sensitivity on a molecular level?
- Why, following hibernation, is pTau not left in situ if it provides a solid-state representation of established engrams?
- Why does ApoE genotype not impact memory and cognition more strongly earlier in life?
- Why has reducing $\text{A}\beta_{42}$ levels not had more profound cognitive effects, even negative ones, in clinical trials?

Questions and avenues for further investigation:

- To what degree do physiological and pathological actions of $\text{A}\beta$ overlap?
- How does sex impact specific mechanisms of $\text{A}\beta$ action?
- What homeostatic mechanisms exist to prevent against over-aggregation?
- How could $\text{A}\beta_{42}$ aggregation be precisely regulated to protect plasticity?
- How are $\text{A}\beta_{42}$ and $\text{oA}\beta_{42}$ levels detected to modulate processes such as sleep?
- What causes overexcitation in AD?
- Why do cholinergic neurons degenerate early in the disease?
- Why are the phenotypes of APP, MAPT and BACE1 knockout mice so mild?
- What are the roles of the many APP-derived products?
- What role, if any, do other $\text{A}\beta$ binding sites play?
- What process or processes deliver the deathblow to neurons and how?
- What is the physiological purpose of the non-amyloidogenic pathway?
- How does the current hypothesis explain other cellular perturbations found in AD, e.g., neuroinflammation, mitochondrial dysfunction, endoplasmic reticulum stress, oxidative stress and microglial infiltration?
- What are the roles of $\text{A}\beta$ and tau in presynaptic compartments?
- How do the effects of intracellular versus extracellular $\text{A}\beta$ differ?
- What role do glia play in determining stability in memory circuits through modulation of aggregating proteins?
- How would pTau and pTau aggregates protect or re-establish plasticity during or following insults?
- How can preclinical models of AD be improved and made more valid?
- How could overloading of memory circuits be prevented?
- How reversible are the pathologies? What are the safest and most effective strategies?
- Do other/all aggregating proteins implicated in dementia and neurodegeneration function in establishing and maintaining changes in neuroplasticity?

25. Concluding remarks

In the space of just four human generations, a split second in its evolutionary timeline, humankind has put humans on the moon, invented the internet, computers and the smartphone, sequenced the entire human genome, ridded the planet of some of the most devastating infectious diseases, devised general relativity and quantum mechanics, invented nuclear power and weapons and produced innumerable feats of art. One wonders how human mental capacity could keep pace with the information age and such achievements. Humans rely more and more on machines with processing capabilities beyond their own to perform tasks from predicting the weather to even seeing into their own brains. They develop artificial intelligence and machine learning so that they can pass over tasks beyond their mental capabilities to the machines and tools they invented. Though the notion that humans have reached a point where their limited mental capacity may be instrumental in their mortality may sound like the material of science fiction, one must recall that dementia may not be the only result of a disparity between human evolution and its achievements. One could easily argue that obesity, diabetes, arthritis, cardiovascular disease, tooth decay and even presbyopia are products of an existence made possible through the technology humankind has invented.

Much of my discussion has focused on PRNP as a cellular receptor that could mediate the effects of A β on very long-term memory. However, it is important to stress that this focus is not intended to be absolute. Rather, it is based on *available* evidence to present a *possible* and *representative* mechanism, one that may serve more as a stereotype than an archetype. More important is the general prediction that A β is fundamental to maintaining and protecting long-term memory. And, overaccumulation of A β -tagged memories underlies a pathological process. Based on available evidence alone, there are many other means by which A β could impact memory, some of which have been discussed. Additionally, many of the ideas presented here are far from unprecedented. Others have speculated that “misfolding” proteins shape and optimize circuits for lifelong plasticity. Kandel’s group working particularly on CPEB3 explicitly hypothesize prion-like molecules stabilize long-term memory (Si and Kandel, 2016). Recent studies show that oligomerization of Orb2 controls enduring changes in synaptic activity and memory (Khan et al., 2015). Clayton and George suggest the presence or absence of α -syn determines synaptic turnover and reorganization in songbirds, guarding against further experience after the end of the critical period for song learning, speculating that α -syn may be part of a STC mechanism (Clayton and George, 1999). Tompa and Friedrich suggest by virtue of its autocatalytic properties, prion protein may act as a bi-bistable switch encoding information such as memory (Tompa and Friedrich, 1998). Others have proposed that A β acts in a negative feedback capacity preventing overexcitation of neurons (Kamenetz et al., 2003), emphasizing that A β is not simply “neurotoxic junk” or “garbage” but important to synaptic plasticity (Koudinov and Berezov, 2004; Puzzo and Arancio, 2013). Nehls commented that the effect of A β on memory is dose dependent with higher concentrations “preserving new memory traces from being overridden by subsequent events that are to be memorized”, though the basis of this statement was not elaborated (Nehls, 2016). Many studies implicate A β in metaplastic events (Galanis et al., 2020; Gilbert et al., 2016; Jang and Chung, 2016; Li et al., 2017a; Megill et al., 2015; Peineau et al., 2018) and Puzzo’s group suggest that by inducing conversion of early LTP to late LTP, oA β ₄₂ plays a part in synaptic tagging (Gulisano et al., 2019). Parihar and Brewer emphasize the modulatory effects of A β on neuroplasticity, noting that aging and A β independently decrease neuronal plasticity, also pointing out that A β -induced neurotoxicity is age-dependent and that the longevity of humans may contribute to AD by rendering the brain vulnerable to A β -induced neurotoxicity (Parihar and Brewer, 2010). In an article published two decades ago, noting that AD particularly impacts brain areas serving higher brain function, Arendt noted: “Life events that place an additional burden on the plastic capacity of the brain or that require a particularly high plastic capacity of the brain might trigger the onset of the disease or might stimulate a more rapid progression of the disease.” (Arendt, 2001). Arendt did not elaborate

greatly on what these life events might be, but also commented that consequently acquiring AD is inevitable with enough time.

Here, I have focused discussion on protein aggregation and maintenance of memory in AD. I have made little discussion of many important known cellular aspects of AD pathology such as perturbations in autophagy, Ca^{2+} homeostasis, mitochondrial dysfunction, glial responses, endoplasmic reticulum stress, insulin physiology, neuroinflammation, infection and several risk factors. I also have not discussed the finer details of processes that may be directly relevant such as phosphorylation or other post-translational modifications of specific epitopes of tau, roles of different tau isoforms, the known effects of APP-derived products other than $\text{A}\beta$ (and even here I have largely focused only on $\text{A}\beta_{42}$), cognitive and affective symptoms such as confabulation, depression and apathy or the limitations of the experimental models from which much of our understanding of AD has been derived. Nor have I extensively discussed relationships with other aggregating proteins such as α -syn, Huntingtin, TDP-43, SOD1, Parkin and transthyretin. I have also not commented on the finer details of the spatiotemporal of $\text{A}\beta_{42}$ or pTau deposition. I have avoided discussing diagnosis and classification of AD and the growing realization that aging brains deposit a wide range of aggregating proteins. These subjects are certainly highly worthy of consideration but in the interest of focus and space they have not been covered extensively. Finally, I have refrained from commenting on prospective therapeutic approaches until more direct evidence supporting the core hypothesis is gained.

Currently PubMed returns over 170,000 citations from a rudimentary search of the word “Alzheimer’s” alone of which around 20% are categorized as reviews. A 2009 article reported that near a fifth of publishing neuroscientists have published an AD-related article (Sorensen, 2009). How could one assimilate this information into a coherent and accurate explanation of AD? It seems almost absurd to think that the human brain has the processing power and memory capacity to understand itself. And what irony it would be that the act of doing so causes its own destruction! Nonetheless, this burgeoning mass of information does not negate the possibility that a simple explanation underlies the cause of AD.

Finally, I acknowledge that the evidence presented here is largely intended to argue in the defense of the hypothesis presented, not in its prosecution, and some of that evidence is based on studies of the neurotoxic not beneficial effects of $\text{A}\beta$. Furthermore, despite the information-rich age we live in, as Newton pointed out: “What we know is a drop, what we don't know is an ocean”. I entertain the possibility that the key to unlocking understanding AD is yet to be found. Nonetheless, I hope that the hypothesis presented here stimulates discussion and helps illuminate the way to treating this devastating and fearsome condition.

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Conflicts of interest

The author declares no conflicts of interest.

Abbreviations

Ach, acetylcholine; **AD**, Alzheimer's disease; **Adora2A**, adenosine receptor 2a; **AICD**, APP intracellular domain; **AMPA**, AMPA receptor; **AMPK**, 5' AMP-activated protein kinase; **APLP1**, amyloid-like protein 1; **APLP2**, amyloid-like protein 2; **ApoE**, apolipoprotein E; **APP**, amyloid precursor protein; **APPs β** , secreted amyloid precursor protein ectodomain β ; **Arc**, activity regulated cytoskeleton associated protein; **ASD**, autism spectrum domain; **A β** , amyloid β (generic term for all isoforms and monomeric/oligomeric states); **A β ₄₀**, amyloid β ₁₋₄₀ isoform; **A β ₄₂**, amyloid β ₁₋₄₂ isoform; **BACE1**, β -site APP cleaving enzyme 1; **BACE2**, β -site APP cleaving enzyme 2; **BDNF**, brain-derived neurotrophic factor; **BIN1**, bridging Integrator 1; **CaMKII**, calcium/calmodulin-dependent protein kinase II; **CDK5**, cyclin dependent kinase 5; **CJD**, Creutzfeldt-Jakob disease; **CLU**, clusterin (apolipoprotein J); **CPEB**, cytoplasmic polyadenylation element binding protein; **CREB**, cAMP response element-binding protein; **CTF β** , C-terminal fragment of APP; **eEF1/2**, eukaryotic translation elongation factors 1/2; **EphB2**, EPH receptor B2; **ERI3**, ERI1 exoribonuclease family member 3; **ERK1/2**, extracellular signal-regulated kinases1/2 (mitogen-activated protein kinases [MAPK]3/1); **FAD**, familial Alzheimer's disease; **FMRP**, fragile X mental retardation protein; **FTD**, frontotemporal dementia; **FTLD**, frontotemporal lobar degeneration; **Fyn**, FYN proto-oncogene, Src family tyrosine kinase; **Glu**, glutamate; **GluR1/2/6/7**, glutamate ionotropic receptor AMPA type subunits 1/2/6/7; **GM1**, monosialotetrahexosylganglioside; **GPR126**, adhesion G protein-coupled receptor G6; **GRB2**, growth factor receptor bound protein 2; **GSK3 β** , glycogen synthase kinase 3 β ; **Homer 1a**, homer scaffold protein 1A; **HSP70**, heat shock protein 70; **HSP90**, heat shock protein 90; **IDE**, insulin degrading enzyme; **KIBRA**, WW and C2 domain containing 1 (WWC1); **LC**, locus coeruleus; **LOAD**, late onset Alzheimer's disease; **LRP/LR**, 37 kDa/67 kDa laminin receptor; **LilrB2**, leukocyte immunoglobulin-like receptor B2; **LRP1**, low density lipoprotein receptor-related protein 1 (apolipoprotein E receptor, α 2-macroglobulin receptor); **LRP/LR**, 37kDa/67kDa Laminin Receptor; **LTD**, long term depression; **LTP**, long term potentiation; **MAP1**, microtubule associated protein 1; **MAPT**, microtubule associated protein tau; **mA β ₄₂**, monomeric amyloid β ₁₋₄₂ isoform; **MEF2**, monocyte enhancement factor 2; **mGluR**, metabotropic glutamate receptor; **mTOR**, mechanistic target of rapamycin kinase; **NCAM**, neural cell adhesion molecules; **NE**, norepinephrine; **NFT**, neurofibrillary tangle; **NMDAR**, NMDA receptor; **NOS**, nitric oxide synthase; **oA β** , oligomeric amyloid β (generic term for all isoforms); **oA β ₄₂**, oligomeric amyloid β ₁₋₄₂ isoform; **P75NTR**, p75 neurotrophin receptor; **PGC-1 α** , peroxisome proliferator-activated receptor gamma coactivator 1 α ; **PGRMC1**, Sigma-2/progesterone receptor membrane component 1; **PI3K/Akt**, phosphatidylinositol 3-kinase/protein kinase B; **PirB**, leukocyte immunoglobulin-like receptor B3; **PKA**, protein kinase A; **PKC**, protein kinase C; **PKM ζ** , protein kinase M ζ ; **PLC**, phospholipase C; **PRPC**, cellular prion protein; **PSD**, post-synaptic density; **PSEN1**, presenilin-1; **pTau**, phospho-tau; **Pyk2**, protein tyrosine kinase 2 β ; **RAGE**, advanced glycosylation end-product specific receptor; **RBM3**, RNA binding motif protein 3; **Sirt1**, sirtuin 1; **SOD1**, superoxide dismutase 1; **SORL1**, sortilin related receptor 1; **STC**, synaptic tagging and capture; **STEP**, striatal-enriched tyrosine phosphatase; **STI1**, stress induced phosphoprotein 1; **STUB1**, STIP1 homology and U-box containing protein 1; **TDP-43**, TAR DNA binding protein; **tPA**, tissue plasminogen activator; **TREM2**, triggering receptor expressed on myeloid cells 2; **TrkB**, tropomyosin receptor kinase B (tyrosine receptor kinase B) or BDNF/NT-3 growth factors receptor) **α 7NicR**, α ₇ nicotinic receptor; **α -syn**, α -synuclein; **5-HIAA**, 5-hydroxyindoleacetic acid; **5-HT**, serotonin

Table 1: Putative PRPs and their functions. See table of abbreviations for explanation of abbreviations. (See Abraham, 2008; Martin and Kosik, 2002; Moncada et al., 2015; Okuda et al., 2020; Rogerson et al., 2014).

Molecule	Candidacy	Primary locality	Aggregating?	Putative function	Notes	Example references
Actin	High	Intracellular	Aggregating	Sets LTD synaptic tag.	Interacts with APP, presenilin and tau.	(Elie et al., 2015; Szabo et al., 2016; Ward et al., 2010) (see Lazaro-Dieguez et al., 2008; Martin and Kosik, 2002; Okamoto et al., 2009; Pinho et al., 2020; Verdile et al., 2007)
Arc	High	Intracellular, extracellular	Aggregating	Regulates many plasticity related genes.	Evidence of transcellular spread. Translocated into activated synapses.	(See Asok et al., 2019; Korte and Schmitz, 2016; Nikolaenko et al., 2018)
BDNF	High	Extracellular	Aggregating?	Regulates PRP synthesis and cytoskeletal changes.	Related to synaptic scaling.	(Fujimoto et al., 2012) (Lu et al., 2011) (see Fernandes and Carvalho, 2016 ; Korte and Schmitz, 2016)
CAMKII	High	Intracellular	Aggregating?	Activation initiates tag-setting.	Broad-range kinase capable of autophosphorylation	(Barcomb et al., 2015) (See Lisman, 2017; Okamoto et al., 2009; Redondo and Morris, 2011; Sanhueza and Lisman, 2013)
CPEB3	Putative	Intracellular	Aggregating	Mediates protein synthesis required for long-term memory storage.	Interacts with actin.	(Fioriti et al., 2015; Stephan et al., 2015)
eEF1 α	Low	Intracellular, extracellular	Non-aggregating	Essential for late-phase long-term facilitation.	Interacts with actin.	(Giustetto et al., 2003; Tsokas et al., 2005)
GluR1	Moderate	Transmembrane	Able to cluster	Ionotropic glutamate receptor subunit.		(See Moncada et al., 2015; Rogerson et al., 2014)
GluR2	Low	Transmembrane	Able to cluster	Ionotropic glutamate receptor subunit. Implicated in synaptic scaling.		(Gainey et al., 2009; Park et al., 2019) }
Homer 1a	Moderate	Intracellular	Non-aggregating	Controls PSD remodeling and Ca ²⁺ signaling.	Interacts with mGluR5.	(Chokshi et al., 2019; Marton et al., 2015; Okada et al., 2009) (see

						Clifton et al., 2019)
KIBRA	Moderate	Intracellular	Non-aggregating	Regulates structural plasticity.	Interacts with PKC/Mζ, AMPARs, tau.	(Heitz et al., 2016; Hu et al., 2017; Makuch et al., 2011; Tracy et al., 2016) (see Schneider et al., 2010)
Neuropsin	Low	Intracellular, extracellular	Non-aggregating	Promotes LTP.	Signals to actin and voltage-dependent Ca ²⁺ channels. Particularly expressed in entorhinal cortex and some cortical areas.	(Ishikawa et al., 2008)
PKMζ	High	Intracellular	Non-aggregating	Necessary and sufficient for maintenance of late-LTP	Undergoes autophosphorylation, persistently active kinase. Regulates AMPAR trafficking.	(See Asok et al., 2019; Lisman, 2017)

Table 2: A β interaction partners. Over 40 different A β interaction partners have been reported. See table of abbreviations for explanation of abbreviations. (See Ferreira et al., 2015; Goure et al., 2014; Jarosz-Griffiths et al., 2016; Li et al., 2017b; Mroczko et al., 2018; Smith and Strittmatter, 2017; Xia et al., 2016).

Molecule	Notes	Selected references
α_{2a} -adrenergic receptor	A β redirects NE signaling to activate GSK3 β and tau phosphorylation. Promotes A β production via SORL1.	(Chen et al., 2014; Zhang et al., 2020)
α_7 NicR	Dose-dependent activation and inhibition. Protects at low A β concentrations? Bestows particular vulnerability of Ach neurons? Impacts NMDAR internalization via calcineurin?	(See Brody and Strittmatter, 2018; Xia, 2016 #1217; D'Andrea and Nagele, 2006; Lasala et al., 2019; Mroczko et al., 2018; Puzzo et al., 2015a; Sadigh-Eteghad et al., 2014; Smith and Strittmatter, 2017)
α B-crystallin	Modulates A β aggregation.	(Narayanan et al., 2006; Raman et al., 2005)
AMPA	Internalization induced by A β via calcineurin.	(See Findley et al., 2019; Mroczko et al., 2018)
ApoE	Modulates A β clearance. May not actually bind A β . Variants linked to LOAD.	(Strittmatter et al., 1993; Verghese et al., 2013) (see Kanekiyo et al., 2014)
β_2 -adrenergic receptors	Induces hyperactivity of AMPARs.	(Wang et al., 2010a) (see Mroczko et al., 2018; Xia et al., 2016)
Calmodulin	Retards A β fibrillation.	(Corbacho et al., 2017) (see O'Day, 2020; O'Day et al., 2015)
Cholinesterase	Induces fibril formation and forms toxic complex	(See Inestrosa et al., 2005)
Complement C1q	Binding triggers complement cascade. Modulates A β aggregation.	(Webster et al., 1995) (see Crehan et al., 2012; Dalakas et al., 2020)
EphB2	Potentially influences NMDA-dependent synaptic plasticity.	(See Li et al., 2017b; Mroczko et al., 2018; Smith and Strittmatter, 2017)
GM1	May promote A β aggregation but also neuroprotective against A β . Binds PRPC.	(Mattei et al., 2020) (See Cebecauer et al., 2017)
Insulin receptor	Altered Insulin signaling implicated in AD. Interacts with SORL1.	(See Folch et al., 2018; Gabbouj et al., 2019; Mroczko et al., 2018; Smith and Strittmatter, 2017)
LilrB2	Mediates inhibitory action of oA β on LTP.	(Kim et al., 2013; Smith et al., 2019; See Smith and Strittmatter, 2017)
LRP1 (contested)	Binds ApoE. Interacts with PRPC. Modulates APP production and clearance.	(Mattei et al., 2020; Van Gool et al., 2019) (see Shinohara et al., 2017)
NMDAR	Function heavily impacted and implicated in synaptotoxicity but unclear if direct binding exists. Also impacted by α -syn.	(Navarria et al., 2015) (see Findley et al., 2019; Li and Selkoe, 2020; Liu et al., 2019a; Mroczko et al., 2018)
Nogo-66 receptor	Important receptor in constraining plasticity. Involved in A β clearance. APP binding partner.	(See Mironova and Giger, 2013; Park and Strittmatter, 2007; Xu et al., 2015)
mGluR5	Group I mGluR widely implicated in synaptic plasticity. Evidence of sex-dependent binding.	(Abd-Elrahman et al., 2020a)
PGRMC1 (Sigma-2)	Modulates sleep proportional to A β length.	(Izzo et al., 2014; See Jarosz-Griffiths et al., 2016; Ozcan et al., 2020; Smith and Strittmatter, 2017)
p75NTR	BDNF receptor. Modulates tau phosphorylation. Ectodomain neuroprotective. Heavily expressed in basal forebrain. Potential APP binding partner.	(Patnaik et al., 2020; Saadipour et al., 2018; Shen et al., 2019; Wang et al., 2011; Yao et al., 2015) (see Mroczko et al., 2018;

	Favors β -secretase activation. Modulates A β aggregation.	Patnaik et al., 2020; Smith and Strittmatter, 2017)
PirB	Immuno-inhibitory receptor. Implicated in synaptic plasticity.	(See Li et al., 2017b; Mroczko et al., 2018; Xia et al., 2016)
PRPC	Mediates neurotoxicity. Complexes with mGluR5. Also binds α -syn.	(Ferreira et al., 2017; Smith et al., 2019)
RAGE	Participates in A β transport across blood-brain barrier.	(See Mroczko et al., 2018; Smith and Strittmatter, 2017; Yan et al., 2009)
Sortilin-Related Receptor 1	Cognition-associated gene. Associated with AD. Involved in APP trafficking. Interacts with BDNF signaling.	(See Barthelson et al., 2020; Houlihan et al., 2009; Smith and Strittmatter, 2017)
TREM2	Variants linked to LOAD. Binds ApoE and clusterin. Mediates mitochondrial damage, aggravated inflammation and cytotoxicity. Involved in synaptic pruning.	(See Agrawal and Jha, 2020; Deczkowska et al., 2020; Mroczko et al., 2018)

Table 3: Select PRPC interaction partners. Note that this table is not intended to be exhaustive nor does inclusion of a molecule necessarily implicate a known relationship in AD or neuroplasticity. Notes largely reflect AD-related interest in the molecules though the consequence of the interaction with PRPC is often unclear. See table of abbreviations for explanation of abbreviations. (See Aguzzi et al., 2008; Castle and Gill, 2017; Didonna, 2013; Liebert et al., 2014; Linden, 2017; Miranzadeh Mahabadi and Taghibiglou, 2020; Puig et al., 2020; Sorgato et al., 2009; Steinert, 2015; Watts et al., 2018; Wulf et al., 2017).

Molecule	Notes	Selected references
14-3-3 proteins	Part of AICD interactome. Interacts with GSK3 β and tau and several Parkinson's disease-related proteins.	(Foote and Zhou, 2012; Satoh et al., 2005)
A β	Mediates neurotoxicity via formation of PRPC-mGluR5-oA β ₄₂ complex.	(Corbett et al., 2020) (see Smith and Strittmatter, 2017)
α_7 NicR	Ach receptor with critical role in learning. Implicated in cholinergic loss and alterations in synaptic plasticity.	(Parri et al., 2011)
α -syn	Interacts with PRPC/mGluR5 and NMDAR2B. Interacts with tau and actin. Displays prion-like spread.	(Corbett et al., 2020; Ferreira et al., 2017; Oliveira da Silva and Liz, 2020)
α B-crystallin	α B-crystallin modulates A β aggregation.	(Sun et al., 2005; Xu et al., 2008)
ApoE	Apolipoprotein regulating fat metabolism. AD-associated risk gene. Involved in A β clearance.	(Gao et al., 2006)
APP	A β precursor. Interaction regulates APP cleavage and affects cell adhesion and CNS development.	(Kaiser et al., 2012; Schmitz et al., 2014)
BACE1	Implicated in synaptic scaling and neurite outgrowth. Directs APP processing towards amyloidogenic processing. Regulated by the AD-risk gene BIN1.	(Miyagawa et al., 2016; Petrus and Lee, 2014; Zhang and Song, 2013)
BCL-2	Protein modulating apoptosis. Interacts with α_7 NicR function.	(Dawe et al., 2019) (See Miranzadeh Mahabadi and Taghibiglou, 2020)
Clusterin/ApoJ	Chaperone protein. AD-associated risk gene. Target of AICD interactome. TREM2 ligand. Inhibits A β and α -syn aggregation. Modulates NF- κ B (NF- κ B implicated in adult neurogenesis and structural plasticity).	(Essabani et al., 2010; see Foster et al., 2019; Kogel et al., 2012; Lenzi et al., 2020; Xu et al., 2008)
Copper	Modulates transduction through and interaction with NMDARs. Modulates A β aggregation and turnover. Possible AD risk factor. Interacts with APP.	(Haigh et al., 2009; Hane et al., 2013; Singh et al., 2013; You et al., 2012) (see Varela-Nallar et al., 2006; Wild et al., 2017)
PINT1 (ERI3)	Polymorphisms associates with educational attainment.	Okbay, 2016 #1377; Spielhauer, 2001 #1152)
Fyn	Regulates phosphorylation, trafficking, and processing of APP. Interacts with tau. Modulates tau aggregation. Signals downstream of mGluR5. Dephosphorylated by STEP.	(see Briner et al., 2020; Nygaard, 2018)
GluR6/7	Subunits of kainate subtype of glutamate receptors. GluR6/7-mediated neurotransmission modulated by PRPC.	(Carulla et al., 2011)
GPR126 (Adgrg6)	G-protein coupled receptor. Interaction modulates myelination.	(Kuffer et al., 2016)
Grb2	Adaptor protein. Also interacts with Pyk2 (Pyk2 is an AD-associated gene that signals downstream of mGluR5), tau and AICD interactome. Involved in actin-based cell motility.	(Blaukat et al., 1999; Lysek and Wuthrich, 2004; See Miranzadeh Mahabadi and Taghibiglou, 2020; Reynolds et al., 2008)
Integrin- β 1 (CD29)	Cell microenvironment sensors implicated in synapse formation and structural neuroplasticity. Receptor of laminin. Interaction with PRPC implicated in neuritogenesis.	(Kilinc, 2018; Loubet et al., 2012; See Miranzadeh

		Mahabadi and Taghibiglou, 2020)
Laminin	Major component of basal lamina. Inhibits A β aggregation. Implicated in memory consolidation and neurite outgrowth. Interacts with Group 1 mGluRs. Interacts with STI1. Interaction with PRPC promotes axogenesis and modulates plasticity and memory formation.	(Graner et al., 2000; Santos et al., 2013). (see Miranzadeh Mahabadi and Taghibiglou, 2020; Morgan and Inestrosa, 2001)
LRP1	Multifunctional cell surface receptor. Interaction modulates PRPC trafficking.	(Mattei et al., 2020; See Miranzadeh Mahabadi and Taghibiglou, 2020)
LRP/LR	Receptor for laminin. Modulates APP processing. Receptor of and mediates A β ₄₂ internalization. Modulates oA β -PRPC-induced cell death. Interacts with tau.	(Cuttler et al., 2020; Da Costa Dias et al., 2014; Jovanovic et al., 2015; Linden, 2017; See Miranzadeh Mahabadi and Taghibiglou, 2020)
mGluR1	Roles in LTD, LTP, metaplasticity and synaptic depotentiation. Role in sleep?	(da Luz et al., 2020; Wang et al., 2016) (see Abraham, 2008 ; Menard and Quirion, 2012; Miranzadeh Mahabadi and Taghibiglou, 2020)
mGluR5	Roles in metaplasticity, behavioral tagging, cognitive aging, synaptic depotentiation, LTD, homeostatic downscaling, extinction learning, synapse elimination/refinement. Homer1 binding/cross-linking protein. Interacts with STEP and APP. Binds oA β ₄₂ . Promotes tau phosphorylation. Role in sleep? Interaction with PRPC heavily implicated in neurotoxicity. Interaction with PRPC can determine A β binding to mGluR5 dependent on sex.	(Abd-Elrahman et al., 2020a) (see Abraham, 2008; Menard and Quirion, 2012; Miranzadeh Mahabadi and Taghibiglou, 2020; Smith and Strittmatter, 2017)
NCAMs (CD56)	Implicated in synapse formation. Interaction with PRPC implicated in neuritogenesis.	(See Miranzadeh Mahabadi and Taghibiglou, 2020; Washbourne et al., 2004)
NMDARs	Fundamental to excitatory transmission and synaptic plasticity. Bind A β ₄₂ . Interaction with PRPC modulates glycinergic activity at NMDAR and bestows neuroprotection against NMDAR-mediated excitotoxicity.	(see Black et al., 2014; Khosravani et al., 2008; You et al., 2012)
oA β ₄₂	High affinity binding. Complexes with mGluR5. Interaction is (questionably) cytotoxic, modulates LTP and LTD, promotes synapse loss, and phosphorylation of Fyn, NMDAR and tau.	(See Miranzadeh Mahabadi and Taghibiglou, 2020; Smith and Strittmatter, 2017; Zhang et al., 2019b)
PSD95	Key scaffolding protein of post-synaptic density. Forms complexes with NMDARs. Implicated in homeostatic scaling and synaptogenesis.	(Broadhead et al., 2016; See Chowdhury and Hell, 2018; but see Keshet et al., 2000)
STI1	Co-chaperone protein. Regulates actin (actin implicated in synaptic tagging and structural neuroplasticity). Inhibits A β binding to PRPC. Interaction is neuroprotective, induces Ca ²⁺ influx via α_7 NicR promoting neuronal survival and differentiation.	(Beckley et al., 2020; Linden, 2017; See Miranzadeh Mahabadi and Taghibiglou, 2020; Ostapchenko et al., 2013; Santos et al., 2013)
STUB1	Co-chaperone with ubiquitin E3-ligase activity. Regulates tau degradation.	(Dickey et al., 2008; Dickey et al., 2006; Gimenez et al., 2015)
Tau	Binding causes neurotoxicity.	(Corbett et al., 2020; Schmitz et al., 2014; Vergara et al., 2015)

Voltage gated calcium channels	Interaction potentially controls neurotransmitter release.	(See Haigh et al., 2019; Miranzadeh Mahabadi and Taghibiglou, 2020)
Voltage gated potassium channels	Potentially impacts neuronal excitability.	(See Haigh et al., 2019)

Graphical abstract

Figure 1: mRNA expression of the genes AD-related genes pertinent to the current discussion. Three-dimensional reconstruction of mRNA expression of mGluR5, PRNP and GluR2 in mouse brain highlighting predominant expression of AD-related genes in the hippocampus. Data is derived from the Allen Brain Atlas (Allen Institute for Brain Science, 2020). Data represents all densities of expression with thresholds 180 upwards. Abbreviations are described in the accompanying abbreviations list.

Figure 2: Putative cellular pathways mediating Aβ₄₂ effects on neuroplasticity and tau phosphorylation. The schema is intended as an example of how oligomerization of mAb₄₂ to oAb₄₂ may guide cellular processes related to establishing and protecting the plasticity state of post-synaptic neurons. In this schema, binding of mAb₄₂ to PRPC promotes its own oligomerization and complexing with mGluR5 and α₇NicRs. Note also that mAb₄₂ binds and modulates α₇NicRs. Though not fully depicted, oAb₄₂ may act as a scaffold between PRPC and mGluR5. This sets in motion several intracellular events that ultimately limit excitation and refine synapses essentially preventing changes in plasticity state, i.e., write-protecting the synapse. These events may also promote the phosphorylation of tau, which acts to mark the synapse as having undergone a change in plasticity, creating an image of the potentiation state of synapses. The process may be modulated by STEP and STI1. Note that several elements of this example pathway include proteins for which polymorphisms in their genes are associated with familial AD (depicted in purple). Others are putative PRPs (depicted in brown). The schema is not intended to be all-inclusive. Dashed lines indicate interposing events omitted for clarity. For more information see text (and Benarroch, 2018; Brody and Strittmatter, 2018; Kumar et al., 2015; Um et al., 2013; Um et al., 2012; Wang and Zhuo, 2012). Abbreviations are described in the accompanying abbreviations list.

Figure 3: Hypothesized $\text{A}\beta_{42}$ control of synaptic efficacy. (A) mAb_{42} act to potentiate synaptic efficacy (green) in the pM to upper nM range. Beyond this point, mAb_{42} oligomerizes to oAb_{42} and acts in the nM to μM range to protect potentiated synapses from over-excitation and neurotoxicity (yellow). This action manifests as apparent depression/depotentialization. Continued presynaptic input causes oAb_{42} to reach sizes capable of neurotoxic actions (red), causing synaptic loss. Note that it is conceivable that post-synaptic cells could be write-protected in a non-potentiated state by oAb_{42} binding. As such, oAb_{42} -write-protection may serve to prevent non-potentiated synapses from being incorporated into potentiated circuits to for instance, reserve them for future changes in synaptic strength. (B) Additionally, $\text{A}\beta_{42}$ may promote potentiation by encouraging presynaptic release of excitatory neurotransmitters (dashed blue line). Abbreviations are described in the accompanying abbreviations list.

Early stage overaccumulation of $\text{oA}\beta_{42}$ (blue) as neocortical $\text{oA}\beta_{42}$ -write protected long-term memory storage approaches capacity. Tau (red) is transmitted from the LC into the entorhinal cortex whereupon phosphorylation to pTau creates an image of established plasticity in the hippocampal indexing system. Hippocampal-neocortical communication is functional. Long-term memories are accessible and formation of short-term memories is barely impaired.

Continued overaccumulation of $\text{oA}\beta_{42}$ corrupts established neocortical plasticity and prompts pTau transmission through the hippocampus. Impaired ability to copy short-term memories from the hippocampus to the neocortex produces anterograde amnesia. $\text{oA}\beta_{42}$ accumulates in the hippocampal formation as short-term memories cannot be cleared. pTau increases in the LC to supply hippocampal circuits and due to suppression of LC activity to avoid damaging established plasticity.

Saturation of neocortical $\text{oA}\beta_{42}$ -write protected plasticity severely corrupts established long-term memories as $\text{oA}\beta_{42}$ reaches toxic levels prompting pTau deposition to form an image of established plasticity. Retrograde amnesia is significant as referencing and accessing any remaining uncorrupted long-term memories becomes challenging due to overloaded hippocampal networks.

pTau continues to spread through the neocortex to image established plasticity. Severe hippocampal dysfunction due to $\text{oA}\beta_{42}$ accumulation corrupts the indexing system rendering any remaining uncorrupted long-term memories only partially or entirely inaccessible.

Figure 4: Model of functional outcome of $\text{oA}\beta_{42}$ and pTau accumulation throughout development of AD. For sake of visual simplicity tau and pTau are represented as the same color (red). Not presented is that some tau transmission may occur directly in neocortical areas. Additionally, tau transmission from the LC to neocortical areas via the hippocampus may occur along all elements of the hippocampal-neocortical axis, not just via anterior neocortical areas as presented.

Figure 5: Simplified schema of hypothesized Aβ and tau interactions at a local circuit level. Here PRPC is presented as a stereotypical oAβ₄₂ receptor suggested to limit post-synaptic excitation and modulate aggregation of trans-synaptically spreading tau. NE is presented as an example of isodendritic neuromodulator. Ach and 5-HT may take on similar roles. Tau/pTau transmission is presented as occurring in the extracellular milieu though various other mechanisms (e.g., exosomes, tunneling nanotubes) may be a more significant conduit. Abbreviations are described in the accompanying abbreviations list.

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