Dementia: an “enzymatic problem”

REPORT

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Introduction

Dementia is a disease characterized by memory loss (especially of short-term memory), cognitive impairment, the loss of computation abilities, but also behavioral patterns such as the loss of common sense and thus the ability of understand and want (if not detected early). Dementia comes in the form of Lewy Body dementia, as seen in Parkinson's Disease and some Parkinsonian syndromes, non-Lewy body dementia, and Alzheimer's dementia, caused by neurofibrillary tangles, but also prion disease dementia, vascular dementia the most dangerous kind (caused by strokes and with the shortest life-expectancy again if undetected).

What they have in common are these tangles, or plaques of proteins that clutter the brain in diverse regions, but another common feature is the "slow" death or the weakening or deterioration of several enzymes, that lead for example to the production of essential "bricks" to cell membrane walls which form several tissues and are necessary to live. These enzymes go through mutations that make them dysfunctional.

ENZYMES INVOLVED

It is possible to track down the enzymes via another common element, which is that of inquiring which proteins are namely mutated and dysfunctional or simply weak and "unwell". The main proteins affected are in fact glycoproteins, fibrillins, elastins, collagen and become dysfunctional.

From this understanding it is possible to track then the enzymes that are "sick" and that "infect" those same dysfunctional proteins found in the various forms of dementia. It is thus found that mostly, the enzymes involved, are glycosyltransferases, and prolyl hydrolases (or procollagen-proline dioxygenases). It is then found that the glycosyltransferase mutations occur at the Ala82Glu and at the Arg92Cys (p.R92C)¹ level which are surrounded by the amino acids *TKG(E)LQSAI-KSLHS(R)DIN* (pdb code: 1bpl); and thus it can be predicted that analogically, by superimposing the two structures of glycosyltransferase with the prolyl hydrolase², the Gln239 (Q239X) and the lysine (K249) within the sequence of *TDG(Q)LVSQ-KSDSS(K)DIR* (pdb code: 2hbu) we should be able to identify mutants for the same. Scientists have discovered a Gln239 to stop codon mutation of the prolyl hydroxylase, but no mutations on the Lys249 has yet been recognized. The bottom line is that these enzymatic mutations make the organism weak and therefore unable to catalyse reactions properly leading to proline, serine and threonine mutations which are notorious in all neurodegenerative illnesses, and especially dementia disease.

It can be observed that dementia could be linked to diabetes type 2, as a probable cause, because enzymatic "proper" catalysis is dependent on ATP and sugars, particularly ribose, and we all know that the mechanism is impaired in diabetes, particularly due to pancreatic islet damage.

TREATMENT STRATEGY

In the end, defining the main root of these mutations may not be of interest, as they could be caused by an etiological microbial agent, or by physical agents; a nutritional aspect would be more prominent in this case.

The main focus is how to resolve the problem of enzymatic “degeneration” regardless of the cause.

As enzymes cannot be a target of drug design, due to obvious risks, the best approach remains the targeting of the affected amino acids within the proteins involved, which takes less time and is more specific. This is in support to what has been previously accomplished.³

Enzymes again thrive on amino acids as they are proteic molecules, therefore nutrition becomes of primary importance. The right amount of proteins, carbohydrates and lipids all benefit enzymatic health. It is with the diet that the right amount of amino acids are introduced in our organism, and these amino acids are used to create new healthy enzymes.

As to what drugs are effective for dementia, Dabigatran⁴ has shown promising results in the worsening of vascular dementia, which remains the most devastating form. It is plausible, as a consequence of this short study, that Dabigatran’s effectiveness may be linked to its ability to interact with arterial elastins or other proteins (fibrillins, glycoproteins such as the intrinsic factor), perhaps by acting as an enhancer, and by stimulating their function of strengthening parietal walls of small vessels. Dabigatran, also resembles the structure of caffeine, which was notoriously known as a prophylactic for dementia.

Lastly, B₁₂ supplementation, either with the diet, or homeopathically for patients with problems, can help prevent dementia.

Conclusion

Lifestyle changes remain the most important step towards relieving dementia symptoms, but also in its prevention, by adopting a well-balanced diet.

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