Causes for Ivermectin failure in *Aptenodytes Forsteri*

A perspective

Pardis Tabaee Damavandi

[Institutional Affiliation(s)]

Author Note

Copyright © 2021. All rights reserved. No part of this publication may be reproduced, distributed, or transmitted in any form or by any means, including photocopying, recording, or other electronic or mechanical methods, without the prior written permission of the publisher, except in the case of brief quotations embodied in critical reviews and certain other non-commercial uses permitted by copyright law

Abstract

Ivermectin is an anti-helminthic drug that works on humans but not on penguins. This short perspective seeks to understand and offers an explanation to why Ivermectin is unsuccessful on penguins (other avian animals, such as eagles, and more), but has succeeded in the human population. The bioinformatics approach can lead to the potential design of novel derivatives that would be exclusively for veterinary use.

Causes for Ivermectin failure in *Aptenodytes Forsteri*

A perspective

Ivermectin (IVM) is an anthelmintic drug that is employed in the treatment and cure of a wide range of parasitic diseases, particularly nematode infections that often occur when our skin is exposed to the common roundworm. Roundworms can access the skin pores from the soil directly, for example by walking bare feet on a “polluted” beach but also through contaminated food and water.

The mechanism of action of IVM is through the inhibition of the insect’s or parasite’s glutamate-gated chloride channels, which are selectively inhibited by the drug itself, without impacting us, the hosts, toxically.

Ivermectin is made of a Lactone core, surrounded by three “arms”, branched into a Spiroketal, a Benzofuran ring and a disaccharide. Although its success has been huge in the cure of parasitic illness in humans, the same cannot be said for many species of Penguins that have recently been infected drastically by the several types of nematodes, which have led some species of Penguins to nearing extinction. In their case the administration of IVM was unsuccessful in curing the disease. In this short article the cause for this failure is investigated through bioinformatics analytical methods, and conclusions are made that can justify the cause for its failure.

Methods

The sequence of glycine receptor subunit $\alpha 3$ (GLRA3) isoform X₂ of penguin species *Aptenodytes Forsteri* were obtained and superimposed with the crystal structure of the human counterpart

which is bound to the Ivermectin. Although no molecular dynamics was carried out, a preliminary analysis was done through sequence analysis, partly thanks to the high homology between the penguin's GLRA3 and the human one. The penguin receptor is also 100% homologous with that of other species of animals (not just avian, but also some amphibians) and this information is readily available on the protein data bank (PDB).

Analysis outcome

The analysis shows that genetic differences in the GLRA3 receptor of the penguin against the human one, induce a shortening of the penguin GLRA3 structure not allowing Ivermectin to find polar contacts with it. The crystal structure of the human GLRA3 demonstrates interactions between the human GLRA3's Ser267 residue (Figure 1), whilst this contact is lost entirely with the penguin's structure (Figure 2).

If we look closely, we can see that Ser267 is shifted into Ser268 in the penguin's GLRA3 sequence. This shift in position is due to the presence of an extra-amino acid, lysine (K) in position 163 (Penguin), which "robs" Ivermectin's Benzofuran moiety access to the penguin's Ser268, unlike in the human, where Ser267 is more "compacted" and easily accessible. Furthermore IVM finds another interaction with the Gln226 of the human GLRA3, also lost in the penguin receptor due to the distancing provoked by the shift.

It is my belief that this amino acidic difference, thus the extra lysine residue, is key in the failure of Ivermectin interacting with the GLRA3 of the *A. Forsteri*.

Other differences that can be observed and not underestimated either, involve both singular amino acids, as well as the length of the Emperor Penguin's GLRA3 protein sequence (ca. an eighth of its size longer than that of the human).

Figure 1. Crystal structure of Ivermectin (orange) interacting with residues Gln226 (olive green) and Ser267 (cyan balls and sticks) of human GLRA3 (cyan; PDB CODE = 5VDH). The Benzofuran ring is involved in multiple contacts with the two residues which stabilize the molecule and make it effective in therapy on humans.

Figure 2. Superimposition of Ivermectin (yellow) that has lost interaction with Gln226 (out of range) and is in proximity of Ser268 (blue balls and sticks) of Emperor Penguin GLRA3 (blue). The Benzofuran ring is out of range to form multiple contacts, thus failing to stabilize the molecule and make it ineffective in therapy on penguins. (NCBI RefSeq = XP_009270617.2).

M(1)SPSDFLDKLMGR**TM**(14)SGYDARIRPNFKGPPVNVTCNIFINSFGSIAETTM DYRVNIFLRQ**K**(60)**N**(60)
WNDPRLAYSEYPDDSLDLDP SMLDSIWKPDLFFANEKGANFHEVTTDNKLLRIFKNGNVLYSIRLTL**T**(128)
I(128)LSCPMDLKNFPM DVQTCIMQLESFGY**T**(162)**N****K**(162-
163)MNDLIFEWQ**DEAP**(172)**EKGA**(173)VQVAEGLTLPQFLLKEEKDL**R**(190)**C**(191)YCTKHYNTGKFTCIE
VRFHLERQMGGYYLIQMYIPSLILVLSWVSFWINMDAAPARVALGITTVL TMTTQSSGSRASLPKVS YVKAI
DIWMAVCLLFVFSALLEYAAVNFVSR [...]

Figure 3. Sequence differences in the two GLRA3 are highlighted in red (*h. sapiens sapiens*) and in blue (*a. forsteri*).

Structural derivatives

Binding studies of several derivatives could lead to the proposition of novel drug therapy for the penguin. The elongation of the chain linking the Benzofuran ring, with adequate additional rigidity on the elongation itself, and the central lactone core, should improve affinity of potential Ivermectin derivatives in the penguin.

Conclusion

The structure analysis of the superimposed crystal structures of GLRA3 involved in binding the anthelmintic drug Ivermectin of both *A. Forsteri* and *H. Sapiens Sapiens*, reveal not just high homology between the receptors of the two species, but that the extra amino acid, a Lysine (K162) found in the site 162 of the penguin could be why Ivermectin is an ineffective chemotherapeutic agent on the penguin, but not in the human.

No conflicts of interest to disclose.

References

1. Laing, R., Gillan, V., & Devaney, E. (2017). Ivermectin - Old Drug, New Tricks?. Trends in parasitology, 33(6), 463–472. <https://doi.org/10.1016/j.pt.2017.02.004>
2. Kleinertz S, Christmann S, Silva LM, Hirzmann J, Hermosilla C, Taubert A. Gastrointestinal parasite fauna of Emperor Penguins (*Aptenodytes forsteri*) at the Atka Bay, Antarctica. Parasitol Res. 2014 Nov;113(11):4133-9. doi: 10.1007/s00436-014-4085-4. Epub 2014 Aug 28. PMID: 25164274.
3. Huang X, Shaffer PL, Ayube S, Bregman H, Chen H, Lehto SG, Luther JA, Matson DJ, McDonough SI, Michelsen K, Plant MH, Schneider S, Simard JR, Teffera Y, Yi S, Zhang M, DiMauro EF, Gingras J. Crystal structures of human glycine receptor $\alpha 3$ bound to a novel class of analgesic potentiators. Nat Struct Mol Biol. 2017 Feb;24(2):108-113. doi: 10.1038/nsmb.3329. Epub 2016 Dec 19. PMID: 27991902.