

Peer Review Overview

Manuscript Title: “The role of monoamine oxidase A in the neurobiology of aggressive, antisocial, and violent behavior: a tale of mice and men”

Received	27-Dec-2019
1st Decision	13-Mar-2020
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Decision Letter

Manuscript Number: PRONEU-D-19-00083

Title: The role of monoamine oxidase A in the neurobiology of aggressive, antisocial, and violent behavior: a tale of mice and men

Dear Dr Bortolato,

Thank you for submitting your manuscript to Progress in Neurobiology.

We have completed our evaluation of your manuscript. The reviewers recommend reconsideration of your manuscript following major revision. We invite you to resubmit your manuscript after addressing the comments below. Please resubmit your revised manuscript by May 12, 2020.

When revising your manuscript, please consider all issues mentioned in the reviewers' comments carefully: please outline every change made in response to their comments and provide suitable rebuttals for any comments not addressed. Please note that your revised submission may need to be re-reviewed.

To submit your revised manuscript, please log in as an author at <https://www.editorialmanager.com/proneu/>, and navigate to the "Submissions Needing Revision" folder.

Progress in Neurobiology values your contribution and we look forward to receiving your revised manuscript.

Kind regards,

Sabine Kastner, MD, PhD
Editor-in-Chief Progress in Neurobiology

Editor and Reviewer comments:

Reviewer 1

The present review by Kolla and Bortolato presents an impressive wealth of information on the role of MAO for behavior. The title might suggest a fiction alluding to Steinbeck, but the authors have indeed tried to base their review on a massive ground of references, combined with a more speculative part on possible underlying mechanisms behind the well-documented association between MAO genotype and behavior. Speculations in that latter part of the paper of course needs further support, but to this reviewer they contribute to the value of the manuscript.

A few thoughts which are up to the authors to decide upon:

In the first paragraph after the headline "Concluding statements and future directions" I would suggest ... outcomes increased risk for aggression and antisocial symptoms - or, according to the hypothesis of plasticity, even a decreased risk in a favorable environment.

In those appealing speculations it would have been welcome with some remarks on species differences. It is a wide gap between rodents with predominant MAOA in the brain and man with MAOB being dominant - overall 80/20 vs 80/20, which might be of particular importance when dopamine is brought into the discussion. Furthermore, early experiments indicated that when MAOA in rodents in blocked prenatally MAOB seemed to increase correspondingly (Shih and co-workers).

However, the review is to be complimented for its choice of references - not forgetting many of he first ones on the scene. However, I cannot see that Bach et al 1988 showed anything on the peculiar covalent binding of the FAD to the apoprotein - e.g. Orelund 1971

Reviewer 2

Reviewer 2 did not give permission to publish their review.

Author Response Letter

Reviewer 1

The present review by Kolla and Bortolato presents an impressive wealth of information on the role of MAO for behavior. The title might suggest a fiction alluding to Steinbeck, but the authors have indeed tried to base their review on a massive ground of references, combined with a more speculative part on possible underlying mechanisms behind the well-documented association between MAO genotype and behavior.

Response: We thank Reviewer 1 for his/her kind words of appreciation of our article.

Speculations in that latter part of the paper of course need further support, but to this reviewer they contribute to the value of the manuscript.

Response: We concur with the Reviewer. We recognize that our conclusions remain speculative, but our intent was to underscore a number of possible interpretations of the biology undergirding gene x environment interactions in antisocial behavior, based on the available animal literature. These ideas should be understood as potential future research directions, which could potentially improve our understanding of the molecular mechanisms of aggression and antisocial conduct.

In the first paragraph after the headline "Concluding statements and future directions" I would suggest ... outcomes increased risk for aggression and antisocial symptoms - or, according to the hypothesis of plasticity, even a decreased risk in a favorable environment.

Response: Thank you for these suggestions. In this revised version, we introduced the differential susceptibility hypothesis in a specific section of the conclusions [pages 53-54], and explain this possibility in detail, illustrating the available evidence and how animal models may be instrumental for testing this fascinating hypothesis.

In those appealing speculations it would have been welcome with some remarks on species differences. It is a wide gap between rodents with predominant MAOA in the brain and man with MAOB being dominant - overall 80/20 vs 20/80, which might be of particular importance when dopamine is brought into the discussion. Furthermore, early experiments indicated that when MAOA in rodents in blocked prenatally MAOB seemed to increase correspondingly (Shih and co-workers).

Response: We fully concur with this observation. In keeping with these suggestions, we have significantly elaborated on the interspecies differences between humans and mice, which may be quite important when dealing with the issue of dopamine catabolism [page 13, second paragraph; and page 49, second paragraph]. We also discussed the compensation existing between MAOA and MAOB. [page 13, second paragraph].

The review is to be complimented for its choice of references - not forgetting many of the first ones on the scene. However, I cannot see that Bach et al 1988 showed anything on the peculiar covalent binding of the FAD to the apoprotein - e.g. Oreland 1971

Response: The Reviewer is correct that Bach et al., 1988 was not the first group to highlight the discovery of the association between MAOs and FAD. Indeed, the discovery of the FAD-MAOA attachment was based on contributions by Profs. Yasunobu and Oreland between 1966 and 1971. We now acknowledge and cite their work in the present revised version. In addition, the identification of the FAD-containing subunit in a cysteine-containing segment of the protein was made by Prof. Singer in 1971. This work is also cited. Finally, we now clarify that the citation of Bach et al. (as well as Hsu et al. in the same year) was related to the notion that MAOs are bound to the outer mitochondrial membrane through their C-termini [page 12, first paragraph].

Reviewer 2

Reviewer 2 did not give permission to publish their review, therefore the authors' responses are not published either.