Authors' Response to Peer Reviews

Authors' Response to Peer Reviews of "Effects of Ventral Pallidum–Nucleus Accumbens Shell Neural Pathway Modulation on Sucrose Consumption and Motivation in Female Rats: Chemogenetic Manipulation Study"

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KEYWORDS

ventral pallidum; nucleus accumbens shell; chemogenetics; sucrose; feeding behavior; food motivation; palatable food; DREADD; designer receptors exclusively activated by designer drugs

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Round 1 Review

Reviewer C [1]

General Comments

In this paper [2], the authors present an interesting and well-written paper dealing with the effects of stimulation and inhibition of projections from the ventral pallidum to the nucleus accumbens shell on feeding and food reinforced behaviors. The methods used are cutting edge, and my comments and suggestions are relatively minor.

Minor Comments

1. In the third paragraph of the Introduction, the sentence beginning with "Parallelly" is very awkward; I am sure there is a way to word this that does not use "parallelly." Also, the previous sentence could be made clearer as to whether effects on sucrose consumption are found just in female rats.

Response: The paragraph has been reworded for clarity and to minimize its possible awkwardness. Moreover, we believe the current phrasing emphasizes that the results were observed only in female rats.

2. The number of subjects should be listed in the Methods.

Response: In the original manuscript, the number of subjects was listed in the Methods section under the subsection "Immunohistochemistry." The authors recognize that this is an unorthodox location for that kind of information, and now, the number of subjects can be found in the "Subjects" subsection.

3. In the last paragraph of the body of the manuscript, the sentence beginning with "The discrepancies observed across studies of this pathway..." is unfinished, and I am uncertain what the authors intended to say.

Response: The offending sentence has been removed from the paragraph. The authors would like to thank the reviewer for the careful reading of the manuscript.

4. In discussing the differences between the results observed here and those reported by Vanchez et al [3], is it possible that these may reflect the use of "closed-loop" manipulations linked to the occurrence of licking in the Vanchez et al [3] paper, in contrast to the continuous modulation produced here by the use of the DREADD (designer receptors exclusively activated by designer drugs) technique? Also, in this section, the authors could be a bit clearer as to why the techniques used by Vanchez et al [3] would be expected to label a different subpopulation of cells than was the case in this study.

Response: This paragraph has been expanded in an attempt to address Reviewer C's comments. The authors believe that the current version of the manuscript offers a more nuanced discussion of our findings and those of Vachez et al [3].

Reviewer Q [4]

General Comments

The manuscript from Peroutka and Covelo [1] describes the results of chemogenic activation or inhibition of the ventral pallidum–nucleus accumbens shell pathway in adult female rats on sucrose intake (20% sucrose bottle access) versus operant response–provided food pellets delivered on a progressive ratio schedule. The rats were not food restricted. Activation of the pathway decreased sucrose intake while inactivation of the pathway increased sucrose intake. Activation or inactivation did not clearly alter responding for food pellets. The authors provide discussion including an interpretation of the results, such that this pathway is important for sucrose consumption but not motivation for food. This is an interesting study that has some limitations listed below.

Specific Comments

Major Comments

1. Why were only female rats used for this study?

Response: Historically, much of behavioral neuroscience research has focused primarily on males, leading to a lack of understanding of female brain function. While this study could have been conducted in male rats, we decided to use female rats to generate more information about the female rat brain. The authors acknowledge that future studies should consider studying male rats to observe if sex is a relevant variable in the observed behaviors.

2. What was the approximate age of the rats at the start of the study?

Response: The age of the rats at the start of the study has been added to the Methods section.

3. The conclusion of the pathway being relevant for sucrose consumption but not food motivation is reasonable, but it would be stronger if the comparisons were made with sucrose consumption versus sucrose motivation and also food consumption versus food motivation.

Response: This study only uses sucrose as a reward, either in the form of sucrose pellets in the case of the progressive ration task, or 20% sucrose solution in the case of the free-access task. The authors recognize that the use of the term "food" throughout the manuscript might have contributed to some confusion as to the nature of the reward used. In this version, we have minimized the generic use of the word "food" and specified that sucrose was used all along. The authors still believe that the chemogenetic manipulations described in the manuscript affected sucrose consumption but not the motivation to work for food.

Minor Comments

4. Are there more objective data from analysis of the immunohistochemistry? What is presented are representative images, but was there any quantification done?

Response: As described in the Methods, immunohistochemistry was studied qualitatively to assess DREADD (designer receptors exclusively activated by designer drugs) expression in the relevant brain areas. The authors consider this analysis to be sufficient to support the conclusions presented in the manuscript. Future studies could be conducted to assess if the number of DREADD-expressing neurons affects the behavioral outcomes observed, although such studies would require a significantly higher number of animals than those used here.

5. The authors discuss cell types but do not specify the likely type of neurons stimulated in this study; is it possible to do so?

Response: The question of the nature of the cells expressing DREADD is interesting and worth studying in the future. Unfortunately, at this time, it is not logistically possible for the authors to conduct such studies.

Round 2 Review

Reviewer Q [4]

General Comments

The authors have addressed my concerns from the initial draft.

References

1. Wirtshafter D. Peer review of "Effects of Ventral Pallidum–Nucleus Accumbens Shell Neural Pathway Modulation on Sucrose Consumption and Motivation in Female Rats: Chemogenetic Manipulation Study". JMIRx Bio. 2025;3(1):e71626. [FREE Full text] [doi: 10.2196/71626]

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3. Vachez YM, Tooley JR, Abiraman K, Matikainen-Ankney B, Casey E, Earnest T, et al. Ventral arkypallidal neurons inhibit accumbal firing to promote reward consumption. Nat Neurosci. Mar 2021;24(3):379-390. [FREE Full text] [doi: 10.1038/s41593-020-00772-7] [Medline: 33495635]
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Abbreviations

DREADD: designer receptors exclusively activated by designer drugs

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