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Fang-Fang Ji,
Science Editor
Editorial Office
Baishideng Publishing Group Inc

Dear Fang-Fang Ji,

We would like to thank the reviewers for their comments on our manuscript entitled "Pharmacological modulation of cholinergic system: Potential approach to treating cognitive deficits of schizophrenia" which have led to a revised version of the manuscript. We will address the comments by the reviewers in a systematic fashion:

Reviewer 1:

This review aims to explain the roles of the cholinergic system, particularly the muscarinic M1 receptor, in cognitive deficits of schizophrenia and discuss a promising therapy, allosteric ligands, for addressing cognitive impairment in schizophrenia. I have a few comments.

Allosteric modulators of cholinergic system receptors were well reviewed in this paper, and it is better if the authors can mention "allosteric modulators" in the title.

We have amended the title to reflect the focus on allosteric ligands.

The overall structure and the logic of the manuscript are somewhat unclear. The authors discussed four hypotheses associated with the mechanism of schizophrenia lengthily. "The cholinergic hypothesis" and "OVERVIEW OF THE CHOLINERGIC SYSTEM" may be incorporated.

We chose to keep the separation between "The cholinergic hypothesis" and "OVERVIEW OF THE CHOLINERGIC SYSTEM" because we wanted to keep the four hypotheses distinct from the further discussion.

The authors focused too much on the pathophysiology of schizophrenia, but the discussion for the cognitive deficits of schizophrenia was insufficient.

The discussion in this review is primarily focused on the pathophysiology of schizophrenia and how allosteric ligands can be used to redress cognitive deficits. We have included a brief description of the cognitive symptoms of schizophrenia and direct readers to a systematic review for their further edification on page 6.

In the part of CONCLUDING REMARKS, the authors only summarized allosteric modulators of muscarinic M1 receptors is a promising therapy to redress cognitive impairment in schizophrenia, ignoring the roles of the cholinergic system in cognitive deficits of schizophrenia.

We presume that this comment refers to the role of the cholinergic system in other disease states and have amended the section "CONCLUDING REMARKS' on page 16 to reflect their possible utility in this regard.

The legend of figure 2 is lack.

We have amended the figure legend, see page 33.

Reviewer 2:

The article "Pharmacological modulation of cholinergic system: Potential approach to treating cognitive deficits of schizophrenia" I can recommend for a publication in WJP. The manuscript was revised according to reviewer comments. I do not have special remarks.

The authors should only correct some technical faults – capitals of drugs, some grammatical faults..

We have re-read the manuscript thoroughly and addressed all typos and grammatical faults.

Reviewer 3:

Dear author(s): Your work is attractive and the reviewing of the topics approached is in 'increasing-interest' today. However, some points should be improved in order to have a adequate version of this manuscript.

The entire manuscript should be revised in order to avoid typing errors. (catacholaminergic,glutamateric, etc.)

We have re-read the manuscript thoroughly and addressed all typos and grammatical faults.

Please check the use of 'involve' instead of 'implicate'.

We have assessed all uses of involve and corrected them were neccesary, see pages 13 and 14.

I suggest you for checking the content of: Christopoulos A, Changeux J-P, Catterall WA, Fabbro D, Burris TP, Cidlowski JA, Olsen RW, Peters JA, Neubig RR, Pin J-P, Sexton PM, Kenakin TP, Ehlert FJ, Spedding M, Langmead CJ. (2014) International Union of Basic and Clinical Pharmacology. XC. Multisite Pharmacology: Recommendations for the Nomenclature of Receptor Allosterism and Allosteric Ligands. Pharmacol Rev. 66:

918-947. [PMID:25026896] in order to express in adequate form the 'allosteric/allosterism definitions'

We have revised our definitions of allosterism related terminology to the reflect the recomended nomenclature, see page 13.

The aim of pharmacologist-developers and medicinal chemists is target a receptor subtype in highly selective form. There are not specific drugs, yet. But there are advances for designing new molecules with advantageous profile. In this regard, please consider these two articles to be included in your review (Insights into the structural biology of GPCRs impacts drug design for CNS neurodegenerative processes. Farfán-García Eunice D., Trujillo-Ferrara José G., Castillo-Hernández María C., Guerra-Araiza Christian H., Soriano-Ursúa Marvin A. Neural Regeneration Research, 2013; 8(24):2290-302 AND Allosteric modulators of GPCRs: a novel approach for the treatment of CNS disorders. Conn PJ, Christopoulos A, Lindsley CW. Nat Rev Drug Discov. 2009 Jan;8(1):41-54.

We have included these reviews, see page 14.

All the best, Reviewer

Our original manuscript now entitled **"Allosteric modulation of cholinergic system: Potential approach to treating cognitive deficits of schizophrenia"** has been revised to address the comments raised by the three reviewers (*italics*) and therefore we hope that the version of the manuscript we now submit is suitable for publication in The World Journal of Pharmacology.

We look forward to hearing from you.

Shaun Hopper
(On Behalf of the Authors)

Brian Dean