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August 16, 2013

Dear Dr. Jin-Lei Wang,

Please find enclosed the edited manuscript in Word format (file name: 4025-review.doc).

Title: Roles of cholinergic receptors during attentional modulation of cue detection

Author: Joshua A. Burk

Name of Journal: *World Journal of Pharmacology*

ESPS Manuscript NO: 4025

I thank the three anonymous reviewers for the careful evaluation of the original submission. I appreciate the generally positive reviews of the original submission. I have made several changes to address the concerns raised by the reviewers. These changes include the addition of over 30 references. Major changes are highlighted in yellow in the manuscript. My responses to the reviewers' comments are listed in a point-by-point fashion below.

Reviewer 00504909

1. First the author should describe the proposed mechanisms of altered cholinergic transmission in Alzheimer's disease models, with particular focus on the link between Abeta oligomers and specific AchR (alpha 7 and alpha4beta2) to induce synaptic pathology. This would provide a rationale to explain the beneficial effects of ligands acting at specific subtypes of AChR in AD models. Also a general section on the clinical development of cholinergic drugs in cognitive disorders should be added.

Response: A section has been added to address the points by the reviewer (p.5-7).

Reviewer 00503471

1. The most important suggestion is to make more explicitly clear that this paper is mainly related to the attentional functions of the ACh system. First paragraph: "...often organized into anterior and posterior systems..." It is not clear to me to what the author refers to. I would suggest making more clear what these anterior/posterior systems are. In the same sentence the authors refer to 'the actions' of ACh. Does he refer to "selection and subsequent processing of stimuli"? The author mentions that there are numerous theories. Indeed, there are also theories that ACh is critical for learning and memory (Bartus et al). So, the author should make clearer to what specific functions and regions he refers to in the first paragraph. With respect to cortical regions attentional functions I would like to refer to some recent review of Klinkenberg et al. In this review on ACh and attention it is shown that not all cortical regions are implicated in attentional functions.

Response: The first paragraph has been revised to make it clear that the present mini-review focuses on attentional processing and to clarify the cortical regions thought to be involved in attention by adding the Klinkenberg et al. (2011) reference and others

(p.4).

2. With respect to the role of the M1 receptor and cognitive functions/attention, I again would like to refer to a recent publication of Klinkenberg et al where they compared scopolamine and biperiden (M1 antagonist). This study shows no clear effect on attention, but mainly an effect on short-term memory (delayed matching task). So, I don't think that it is very clear that the M1 receptor is involved in attention.

Response: The relevant Klinkenberg et al. (2011) reference has been added and incorporated into the section regarding muscarinic M1 receptor antagonists and attentional processing (p.8).

3. The author states that: "Collectively, the available evidence suggests that decreasing cholinergic receptor activity at multiple subtypes can have a synergistic negative effect on attentional performance and that agonism, increasing the activity of $\alpha 4\beta 2$ nicotinic receptors, can overcome attentional deficits following muscarinic receptor blockade." I am not so sure whether this is a valid statement. There are many drugs that can reverse muscarinic blockade-induced deficits. So, the effects may not be specific or these data suggest that multiple neurotransmitters interact in a functional manner. Furthermore, these effects are not only observed for attentional functions (you have to consider all findings in the literature). Although the author may want to focus on attentional functions, there are many more aspects that are just left out. One way to get around this is to state explicitly that it is appreciated that ACh has many functions, but that the present mini-review only describes the attentional aspects.

Response: The revised manuscript clarifies the focus on attentional function (p.4 & 12). Moreover, a caveat is now included regarding the interpretation of the effects of $\alpha 4\beta 2$ nicotinic receptor agonists on muscarinic receptor blockade with regard to the potential of other drugs to have similar effects (p.12).

4. The alpha-7 receptor has also been implicated in attention (review by Leiser et al). I think this receptor should be mentioned when mentioning nicotinic receptors (much more is described for muscarinic receptors in this manuscript). There is even an alpha-7 compound in phase III of clinical testing, which may reflect the relevance of this target.

Response: The section regarding the alpha-7 nicotinic receptor and attention has been expanded (p.11-12) and the compound in phase III clinical testing mentioned by the reviewer is now included (p.13).

5. In the summary and conclusions it is mentioned that allosteric modulators could be very beneficial for treatment. This is only very briefly described in the body of the text. I think some more explanation should be given in the main text in order to give this statement in the summary and conclusions more body.

Response: The manuscript now briefly introduces allosteric receptor agonists earlier in the document (p.7) and the section regarding allosteric agonists has been expanded (p.13-14).

The formatting, reference style and typesetting have all been updated. Thank you for consideration of this manuscript and I look forward to hearing from you.

Sincerely,

A handwritten signature in black ink that reads "Josh Burk". The signature is written in a cursive, slightly slanted style.

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