Author’s response to reviews

Title: Regulation of urinary bladder function by protein kinase C in physiology and pathophysiology

Authors:
Joseph Hypolite (joseph.hypolite@ucdenver.edu)
Anna Malykhina (anna.malykhina@ucdenver.edu)

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Author’s response to reviews:

We thank the reviewer for the constructive criticism and useful suggestions. We revised the text of the manuscript in accordance with reviewer’s recommendations. All changes made to the text are shown in red font in the revised copy of the manuscript. The detailed responses to the reviewer`s comments are included below.

Reviewer #2

Comment #1. “Methods” section should be written according to the international standards and should describe the strategy used to do the revision of the literature. The actual section is brief and do not include which key words have been used and which databases have been searched.

Response: We revised the Methods section based on the reviewer`s comment, and included the search strategy, key words as well as database references (Abstract and p.3-4).

Comment #2. Results. This section is not present and needs to be written. It should include also a PRISMA flow chart (see BMC Urol. 2014 Oct 27;14:84. doi: 10.1186/1471-2490-14-84. Gacci et al Tolterodine extended release in the treatment of male OAB/storage LUTS: a systematic review).

Response. We appreciate this comment, however, we cannot include this section in our manuscript since it is not a systematic review nor a meta-analysis. We clearly stated in the Methods that our manuscript is a non-systematic review of the literature, therefore, PRISMA statement is not applicable to this type of publication (PRISMA stands for Preferred Reporting Items for Systematic Reviews and Meta-Analyses http://prisma-statement.org).

Comment #3. 'Modulation of DSM excitability and ion channel activity by PKC': The relationship between VGCC and PKC is not very clear and should be better described, in fact the figure 3 seems to show no real connection between PKC and VGCC. Figure 3 should be included as a reference at the end of the paragraph with a line of conclusion summarizing the relationship between ion channels and PKC.
Response. Thank you for this valuable comment. We revised this section accordingly (p.6) and Fig.3 is Fig.2 in the revised manuscript.

Comment #4 (minor). “Functional modulation of bladder innervation by PKC”. The very scarce evidence on this area as stated by the authors make this paragraph of low interest and I would briefly summarize this information in the new discussion section. The paragraph should be deleted.

Response. We have deleted this paragraph, as suggested by the reviewer, and briefly mentioned this information in the Discussion section.

Comment #5 (minor). “Regulation of bladder function by PKC under pathophysiological conditions': From the former paragraph it clearly appears that regulation of PKC is associated with both PBOO and DO. However the paragraph is a little confusing. It is not very clear if animals with DO have lower or higher levels of PKC as the first and the second paragraph seem to affirm the opposite: See page 12 lines 6-10 'inhibition of PKC{…}characterized by an increase in non-voiding contractions(DO)' and see page 12 lines 22-26' High levels of PKC stimulation{…}associated with enhanced nerve-mediated contractions'. The authors should better clarify this point.

Response. Thank you for bringing this issue to our attention. We revised these paragraphs and clarified that PKC expression and activity in PBOO model depends on the species and degree of obstruction. In rabbits, decompensated bladders (PBOO model only) had a reduced PKC expression and activity while compensated bladders exhibited increased PKC expression. However, in rats with PBOO, PKC expression was reduced in both compensated, and decompensated bladders (p. 11).

Comment #6 (minor). Is there any evidence on the role of PKC in detrusor underactivity?

Response. The search of the literature did not find any published data on the relationship between PKC and detrusor underactivity. We have mentioned this in the discussion section focused on study limitations (p. 14).

Comment #7. Conclusions - this section should be reorganized. The second paragraph should be included in the discussion. The first paragraph is well written and represents the Conclusions section.

Response. We have moved the second paragraph to the discussion section, as suggested by the reviewer.

Comment #8. Limitations. A paragraph including the limitations of the former review should be included.

Response. We thank the reviewer for this valuable suggestion. We have included the new paragraph in the discussion section focused on the study limitations (p. 13).
Comment #9. Abstract: A phrase in the background section giving the aim of the study should be added.

Response. We have included the aim of the study in the Background section of the abstract (in red).