Format for ANSWERING REVIEWERS

ESPS Manuscript NO: 15412
Columns: MINIREVIEWS

Title: Species differences in regulation of renal proximal tubule transport by certain molecules

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#Response to Editor,

Thank you very much for careful evaluation of our manuscript. According to the suggestions by reviewers, we made substantial modifications which are highlighted in red.

I hope our manuscript is now improved and suitable for publication.

Sincerely yours

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#Response to Reviewer 00503339

Thank you very much for your comments.

“The Authors would strengthen their case that species differences in renal physiologic response may impact both the presentation of diseases and response to therapy. Clear examples include the recognition of the importance of advanced glycated endproducts in the deleterious effect of induced diabetes in rodents as well as the marvelous blockage of progression of induced diabetic nephropathy by aminoguanidine and a series of other drugs including Alagebrium, Pyridoxamine, and Ruboxistaurin which were not found effective in initial human trials in diabetic patients. The point being made is that the Authors would add to the meaning of their Review by proffering several examples of how metabolic species differences have thus far created substantive problems to the extent that several well known investigators have turned away from using rodents in favor of canines and primates for their important trials.”

According to your suggestions, we added several examples of agents such as aminoguanidine, pyridoxamine, and Ruboxistaurin that are effective in animal models of diabetic nephropathy but not in human patients in pages 5 to 6. We also discussed about usefulness of dogs, pigs, and other primates for toxicology in page 6. Due to these modifications, we added new references 9-19.

“It would also increase the meaning of this Review if the Authors added several summaries within the paper of what is being discussed and which derivative studies might prove productive.”

According to your suggestion, we now added Summary in page 11.

“Lastly, one or two diagrams centering on the Proximal Tubule and the inferences drawn from the studies cited would help Reader understanding. In its present form, there is minimal enthusiasm generated for continuing the quest for further agents to solve the clinical problems of diabetic patients.”

According to your suggestion, we now added Figure 1 and 2 in page 11.

Response to Reviewer 00503043

Thank you very much for your comments.

“1) Title " Maybe Species differences in the transport of certain molecules in the renal proximal tubule" could be more suitable”

According to your suggestion, we now change the title to “Species differences in regulation of renal proximal tubule transport by certain molecules”.

“2) I suggest add content of “WNK kinases regulates the balance between renal NaCl reabsorpion and K+ secretion”some references are following 2.1 Yang CL, Angell J, Mitchell R, Ellison DH. WNK kinases regulate thiazide- sensitive Na-Cl cotransport. J Clin Invest, 2003，111(7):1039-1045. 2.2 Kahle KT, Wilsom FH, Leng Q, Lalioti MD, O’Connell AD, Dong K, Rapson AK, MacGregor GG, Giebisch G, Hebert SC, Lifton RP. WNK4 regulates the balance between renal NaCl reabsorpion and K+ secretion. Nat Genet, 2003，35(4):372-376. 2.3 Kahle KT, Gimenez I, Hassan H, Wilson FH, Wong RD, Forbush B, Aronson PS, Lifton RP. WNK4 regulates apical and basolateral Cl- flux in extrarenal epithelia. Proc Natl Acad Sci U S A, 2004,101(7):2064-2069”

According to your suggestions, we now added discussion about WNK kinase systems in pages 7 and 8, and added new references about WNK (References 32-34).

Response to Reviewer 00502999

Thank you very much for your comments.

“I suggest the title be modified: Maybe "Species differences in the transport (or handling) of certain molecules in the renal proximal tubule" could be more suitable.”

According to your suggestion, we now change the title to “Species differences in regulation of renal proximal tubule transport by certain molecules”.

“When talking about TZDs, authors explain that these drugs have no effect at the distal tubule

(pages 4 and 5). However, at the end of that section they state that ENaC maybe involved in the mechanisms of salt and water retention caused by these drugs (last sentence page 6). Please conciliate and clarify this contradiction.”

To avoid the confusion, we now omitted the discussion about different amiloride effects in page 7. Instead, we here added the discussion about WNK according to the suggestion by Reviewer 00503043.

“Page 9: Main paragraph. From "However, renal NO production...." until "However, such an adaptive...humans" needs to be rewritten. It is repetitive.”

According to your suggestion, we now modified this part in page 11.