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ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
ESPS manuscript NO: 23014
Title: Calcium-sensing receptor: a new target for therapy of diarrhea
Reviewer's code: 02821664
Reviewer's country: Canada
Science editor: Yuan Qi
Date sent for review: 2015-10-14 08:07
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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[ ] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
[ ] Grade C: Good	[ ] Grade C: A great deal of language polishing	[ ] Duplicate publication	[ ] Rejection
[ ] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[Y] Minor revision
[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This review by S. Cheng focuses on the role of calcium-sensing receptors (CaSR) in diarrhea. Clearly, diarrhea is a leading cause of mortality and morbidity, especially in developing countries, and the cost and effect of diarrhea deserve urgent attention. The need for additional therapies is highlighted in this review, given limited efficacy and feasibility of current approaches, especially in children, who are most vulnerable to acute diarrhea. The review does an excellent job of explaining the pathophysiology of diarrhea and how different pathways, mechanisms, and treatments affect this. Most of the review focuses on CaSR. First, the roles of the protein are described, with specific focus on effects on intestinal transport. Detailed studies focused on the role of CaSR in secretion, absorption, specific ion channels, and the enteric nervous system are then presented. Effects on gut inflammation and barrier functions as described as well. Finally, clinical experience using Ca to treat diarrhea in mice and humans is described, together with discussing the translational potential of this pathway. The review is very timely, well written, and provides recent data on CaSR, which I'm sure many of the journal's readers know little about. However, there are a few points that require further attention:
General comments: 1. CaSR certainly seems to have an impressive array of effects on many intestinal

aspects leading to diarrhea. The review includes detailed descriptions of various channels and pathways affected by CaSR but most of these studies are based on observations from cell lines or use of Ussing chambers. There is a need to highlight these limitations and the fact that studying these effects in isolation is artificial. A few mouse studies are mentioned, but these are mainly related to the inflammatory interactions of CaSR. It would be useful to have a description of the phenotype of CaSR-/- mice in a separate section, in order to better define the net effect of the absence of this gene. Do these mice spontaneously develop diarrhea? 2. Are there any reports associating SNPs in CaSR for diarrheal conditions? Most of the reports I could find just showed correlation with Ca serum levels and kidney stones. One would expect that polymorphisms or mutations in such a profoundly involved molecule would lead to clinical conditions. This suggests redundancy with other pathways, which needs to be discussed. 3. Page 18 – Figures 2 & 3 are mentioned but they do now appear anywhere in the review. 4. Page 22 - use of calcium in animal and human studies is indeed well-established to protect against diarrhea but this ion has diverse physiologic roles that need to be considered. How would one go about confirming the specificity of Ca effects to CaSR? Specific comments: 1. Page numbering starts at page 5. 2. Page 9 (of the author's order), last paragraph: the sentence 'Consequently, ORS does not offer a rapid relief of diarrhea symptom' should be toned down; the author makes a good case for the limitations of ORS but it still does have an important role. 3. Page 11, last paragraph: 'While anti-microbial is useful in some cases' – either change to 'anti-microbials are…' or to 'anti-microbial therapy is…' 4. Page 20: there are many ways of classifying mechanisms of diarrhea. The author proposes secretory and diarrhea, but there are also osmotic and mixed causes that should be mentioned. 5. Page 21, bottom of page: I would not say that intestinal CaSR is a mechanism; rephrase.

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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The author discusses modulations of CaSR as anti-diarrheal therapies. Since these modulators seem promising agent, the summary table(s) informing names of agents, efficacy and adverse events (if any) should be provided.