

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 28018

Title: Carbon monoxide contributes to the constipating effects of granisetron in rat colon

Reviewer's code: 03647717

Reviewer's country: Japan

Science editor: Jing Yu

Date sent for review: 2016-06-29 09:21

Date reviewed: 2016-08-05 18:38

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input checked="" type="checkbox"/> Grade A: Priority publishing	Google Search:	<input checked="" type="checkbox"/> Accept
<input checked="" type="checkbox"/> Grade B: Very good	<input type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		<input checked="" type="checkbox"/> No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		<input checked="" type="checkbox"/> No	

COMMENTS TO AUTHORS

Comments to the Author Re: Carbon monoxide contributes to constipating effects of granisetron in rat colon Dear sir, thank you very much for your effort to describe this manuscript. 1. MATERIALS AND METHODS: Mention about age of rat. 2. MATERIALS AND METHODS: You should describe meaning of abbreviations of i.p., s.c.. 3. Result: Following sentences are not Result. Put it in Introduction. ? In line with our previous study[9], acute administration of granisetron increased the time to first defecation. ? In a previous work we did not observe any significant effect of granisetron at concentrations of 0.1, 0.3 and 1 μ M[9]; therefore, a 3 μ M concentration of granisetron was chosen for the present investigation. 4. Illustrate relation of HO/CO pathway, Ach, granisetron and other elements with figures.

ESPS PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology

ESPS manuscript NO: 28018

Title: Carbon monoxide contributes to the constipating effects of granisetron in rat colon

Reviewer's code: 00699919

Reviewer's country: Poland

Science editor: Jing Yu

Date sent for review: 2016-06-29 09:21

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CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
<input type="checkbox"/> Grade A: Excellent	<input type="checkbox"/> Grade A: Priority publishing	Google Search:	<input type="checkbox"/> Accept
<input type="checkbox"/> Grade B: Very good	<input checked="" type="checkbox"/> Grade B: Minor language polishing	<input type="checkbox"/> The same title	<input type="checkbox"/> High priority for publication
<input checked="" type="checkbox"/> Grade C: Good	<input type="checkbox"/> Grade C: A great deal of language polishing	<input type="checkbox"/> Duplicate publication	<input type="checkbox"/> Rejection
<input type="checkbox"/> Grade D: Fair	<input type="checkbox"/> Grade D: Rejected	<input checked="" type="checkbox"/> Plagiarism	<input type="checkbox"/> Minor revision
<input type="checkbox"/> Grade E: Poor		[Y] No	<input type="checkbox"/> Major revision
		BPG Search:	
		<input type="checkbox"/> The same title	
		<input type="checkbox"/> Duplicate publication	
		<input type="checkbox"/> Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

Review of the paper Title: Carbon monoxide contributes to constipating effects of granisetron in rat colon Summary: This manuscript describes an interesting and potentially important series of experiments probing the contribution of heme oxygenase/carbon monoxide (HO/CO) pathway to constipating effects of granisetron. Although the effects of the involvement of HO/CO pathway in granisetron-mediated effects on rat duodenal motility have already been well characterized the novelty of the manuscript is their assessment under modifications of this pathway in rat colon. Following handling/training the animals were randomized to treatment groups and treated with saline, granisetron (25, 50, 75 µg/kg/s.c.) alone or in combination with zinc protoporphyrin IX (ZnPPIX, 50 µg/kg/i.p.) and hemin (50 µM/kg/i.p.) (6-8 animals per group). Granisetron was shown to dose-dependently increase the time to first defecation, which was reversed by ZnPPIX but not modified by hemin. Both ZnPPIX or hemin given alone had no effect on this gastrointestinal motility parameter. The mechanism of action of granisetron was verified by in vitro studies as the contractile neurogenic response to electrical field stimulation (EFS 3, 5, 10 Hz, 14 V, 1 msec, pulse trains lasting 10 sec) as well as the contractile myogenic response to acetylcholine (ACh, 0.1 - 100 µM) of colon

specimens incubated with granisetron (3 μ M, 15 min) alone or in combination with ZnPPiX (10 μ M, 60 min) or CO releasing molecule-3 (CORM-3, 100, 200, 400 μ M). Granisetron given alone (3 μ M) did not significantly modify the colon contractile response to either EFS or ACh. ZnPPiX given alone (10 μ M) significantly reduced the colon contractile response to EFS (the effect abolished by atropine), but not to ACh, whereas CORM-3 (400 μ M) alone caused atropine-reversible increase contractile response both to EFS (10 Hz) and to ACh (100 μ M). Additionally, a decrease in colon contractile response to EFS by ZnPPiX was abolished by co-incubation with granisetron, whereas co-incubation of granisetron and CORM-3 further increased the colon contractile response to EFS and to ACh.

Major Comments The results presented are intriguing and may offer insight into the relative contribution of the OH/CO system not only to colon motility but also treatment response and side effect of 5HT-3 receptor antagonists. While the paper is interesting it is based solely on electrophysiological measures with only one objective measure of behavioral observations, time to defecation. However, the authors refrain from asking and trying to answer some key questions: 1. What are the effects of the granisetron/ZnPPiX treatment within the serotonergic system? Is the colon response to granisetron/ZnPPiX treatment related to changes in the serotonergic system? 2. It seems necessary to study if alleviation of granisetron-induced constipation does not lead to reduced antiemetic effects of this drug. 3. Gastrointestinal transit (GIT) should be measured with the use of a nonabsorbable, colored marker given intragastrically. The method to measure GIT used by authors is obviously erroneous. Moreover, how do the authors include to the statistics the differences in the amount of food consumed? In addition, this method does not allow to distinguish differences in the passage through the small intestine and colon. 4. The 180 min observation to first defecation seems to be shorter due to "ceiling effect" of granisetron (most of the animals do not defecated at this time). These are all fairly general statements, but at least some mechanisms and direct cause - effect data must be added to the manuscript.

Minor Comments 1. Introduction - phrase (see[15] for references) should be ... (see[15] for review) 2. The NG-nitro-L-Arginine (L-NNA) and atropine effects are not introduced in the Abstract and Introduction sections - please do so. 3. Results section should be clarified and rearranged mainly in the aspect of statistic