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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34441
Title: The human small intestine is capable of rapidly restoring barrier function after short periods of ischemia
Reviewer's code: 00832047
Reviewer's country: Denmark
Science editor: Ya-Juan Ma
Date sent for review: 2017-04-25
Date reviewed: 2017-04-28

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

The manuscript by Schellekens DHSM et al. reports on the ability of the small intestine to rapidly restore the barrier function following a short exposure to ischemia. By subjecting a section of human jejunum of consenting patients undergoing surgery to 30 min of ischemia, they studied barrier loss and recovery during reperfusion periods of 30-120 min. Tissue damage was assessed by microscopy of various markers of epithelial integrity, barrier loss by a dual-sugar absorption test, and plasma citrulline -and glutamine concentrations were determined as a marker for enterocyte function. The authors conclude that the intestine is capable of a rapid morphological and functional recovery following a short exposure to ischemia. Evaluation: Maintenance of the intestinal barrier is an important defense against invasion of luminal pathogens, and assessment of barrier function is relevant in a number of diseases of the gut where the barrier is compromised. The paper presents some interesting in vivo data showing the ability of the jejunal epithelium to recover rapidly following ischemic injury. Overall, the

study is well designed and sound. However, the conclusions could be strengthened by addressing the following points: Page 4, last sentence of abstract: "Data from DST and citrulline closely parallel…" Yet, it is puzzling that the DST is at baseline level at 30I and only increased at 30I30R (Fig. 3C), whereas the Citr/Gln ratio is only decreased at the 30I time point and not during reperfusion. The authors should discuss this apparent discrepancy and maybe adjust their conclusion. Fig. 3B: The contrast of the image showing the 30I120R time point is rather poor and should be replaced, as it does not reveal the lateral membranes between the cells. Fig. 4: Only ratios of citrulline/glutamine are presented, so is the drop at 30I solely due to a decrease in venous citrullline? For clarification, a comprehensive table showing all the V- and A measurements should be provided. The attached ethical approval document dated 08-10-2012: I am not at all familiar with the Dutch system, but to me the document looks like an application for ethical approval. Has approval also been granted? Minor point: Unclear sentence on p. 3, line 10: "… function were measured of function enterocytes restoration."

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34441
Title: The human small intestine is capable of rapidly restoring barrier function after short periods of ischemia
Reviewer's code: 00055041
Reviewer's country: Italy
Science editor: Ya-Juan Ma
Date sent for review: 2017-04-25
Date reviewed: 2017-05-03

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[Y] Grade A: Priority publishing	Google Search:	[Y] Accept
[Y] Grade B: Very good	[ ] Grade B: Minor language polishing	[ ] The same title	[ ] High priority for publication
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[ ] Grade E: Poor		[Y] No	[ ] Major revision
		BPG Search:	
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		[ ] Duplicate publication	
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		[Y] No	

COMMENTS TO AUTHORS

The paper is interesting and is well written and generally results support the conclusions

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34441
Title: The human small intestine is capable of rapidly restoring barrier function after short periods of ischemia
Reviewer's code: 00055095
Reviewer's country: Hungary
Science editor: Ya-Juan Ma
Date sent for review: 2017-04-25
Date reviewed: 2017-05-08

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
[ ] Grade B: Very good	[Y] 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
[Y] Grade D: Fair	[ ] Grade D: Rejected	[ ] Plagiarism	[ ] Minor revision
[ ] Grade E: Poor		[Y] No	[Y] Major revision
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		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

The aim of this descriptive human study was to extend the scope of previous works of the research group (Am J Pathol 2010, WJG 2016) and to confirm the presence and consequence of reperfusion injury in the human gut. According to the authors only few human experimental studies exist that directly correlate barrier function to histological appearance. This is true, and in this sense the novelty is certainly questionable, but the study is well-planned and executed and deserves further attention. Nevertheless, there are some problems also which limit the conclusions that can be drawn from this investigation. Major 1. The study was approved by an ethics committee –please provide exact reference number here. 2. Patients undergoing pancreatico-duodenectomy were included to assess mucosal permeability and mucosal structural changes, and the authors concluded that the "study directly correlates histological data with intestinal permeability tests". This statement is misleading. The authors performed immunohistochemistry and electron microscopy to visualize certain changes linked to

tight junctions but a direct correlation between these parameters (quantitative data on functional and structural damage of the mucosa) is missing. The results of an appropriate statistical analysis (with probability values) testing the association between permeability data and structural mucosal damage should be provided. In other words, the results of a statistical analysis looking for the association between the degree of structural injury (using a semi-quantitative scoring system like the Chiu grading on HE-stained light microscopy sections - and not only immunohistochemistry for tight junctions and electron microscopy of single cells) and functional data should be shown to reach meaningful conclusion. 3. Human clinical data are very important, but it would be equally important to provide a comparison with comparable animal data. In other words, it would be important to correlate these human data with previous data from standardized animal models. Here it should be mentioned that the exact magnitude of ischemia or reperfusion-induced intestinal mucosal damage as a function of the occlusion time was evaluated in standardized animal models of complete segmental arterial ischemia (see e.g. Boros M et al Ischemic time-dependent microvascular changes and reperfusion injury in the rat small intestine. J Surg Res 1995), and besides, the time scale of restoration of barrier function in injured intestinal mucosa is well described as well (e.g. Blikslager AT: Physiol Rev, 87: 545–564, 2007). These important background references should be included and properly discussed. 3. Legends to figure 1, 2 and 3 are erroneous (panels to B and C are changed). 4. Is it possible to generalize these findings to the whole length or other segments of the human GI tract? Isn't there a region-specificity of permeability changes in the human mucosa? Besides, in animals Takeyoshi and coworkers (Transplantation 2001) has shown remarkable differences in the regenerative capacity of the small intestinal sections -regeneration being more pronounced in the jejunum than in the ileum. Again, this possibility should be properly discussed.

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PEER-REVIEW REPORT

Name of journal: World Journal of Gastroenterology
Manuscript NO: 34441
Title: The human small intestine is capable of rapidly restoring barrier function after short periods of ischemia
Reviewer's code: 00641306
Reviewer's country: United States
Science editor: Ya-Juan Ma
Date sent for review: 2017-04-25
Date reviewed: 2017-05-09

CLASSIFICATION	LANGUAGE EVALUATION	SCIENTIFIC MISCONDUCT	CONCLUSION
[ ] Grade A: Excellent	[ ] Grade A: Priority publishing	Google Search:	[ ] Accept
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[ ] Grade E: Poor		[Y] No	[Y] Major revision
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		[ ] The same title	
		[ ] Duplicate publication	
		[ ] Plagiarism	
		[Y] No	

COMMENTS TO AUTHORS

This is a straight-forward paper associating results from lactulose/rhamnose ratios with histology and microscopic observations of the intestine following ischemia reperfusion. Much of what is reported has been demonstrated in animal models, but not before in human tissue. The major issue is the rigor of the microscopy studies. It is unclear if the data presented are reproducible among the additional subjects. Ideally, images should be scored in a blinded fashion. Minor comments: Remove rapidly from the title. Remove "unique" from the conclusions inthe abstract The term DST needs to be defined. The description of Patients in the methods section does not make sense.