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# PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastroenterology
**Manuscript NO:** 34033
**Title:** Protective effects of oral glutathione on fasting-induced intestinal atrophy through oxidative stress
**Reviewer's code:** 03668441
**Reviewer's country:** Spain
**Science editor:** Ze-Mao Gong
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| 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 |
| [Y] Grade C: Good | [ ] Grade C: A great deal of language polishing | [ ] Duplicate publication | [ ] Rejection |
| [ ] Grade D: Fair | [ ] Grade D: Rejected | [ ] Plagiarism | [ ] Minor revision |
| [ ] Grade E: Poor | | [Y] No | [Y] Major revision |
| | | BPG Search: | |
| | | [ ] The same title | |
| | | [ ] Duplicate publication | |
| | | [ ] Plagiarism | |
| | | [Y] No | |

## COMMENTS TO AUTHORS

In this study authors investigate the effects of oral administration of GSH in fasting-induced intestinal mucosal atrophy. Results are interesting because data suggest that oral GSH reversed mucosal atrophy in the jejunum, but the exact mechanism involved in this effect is not fully clear. Thus, there are some important issues that must be addressed. MAJOR POINTS 1. Author's main hypothesis is based on the idea that intracellular GSH levels in the intestinal mucosa are decreased after fasting and oral administration of GSH has been previously shown to restore its levels in deficient tissues. Conversely, they found that oral administration of two doses of GSH further decreases intracellular GSH levels in the jejunum, which correlates with a downregulation of Ggt1 (the enzyme that breaks down extracellular GSH to produce the cysteine used in the cells to resynthesize GSH). An action in extracellular ROS at the intestinal lumen has been proposed but there is not experiments in this study showing this fact, taken into account that every measurement has been performed in mucosal tissues. - How can

we explain that oxidative DNA damage (as indicative of intracellular ROS level) is reduced after GSH administration if intracellular GSH levels are lower than in control mice? - What is the link between extracellular GSH actions and the expression of iNOS (and subsequent NO production)? - Since there is not a measurement of luminal ROS and intracellular ROS and NO synthesis can only reflect the level of damage in the intestinal mucosa, we cannot assume a specific effect of oral GSH. In conclusion, more experiments (in the discussion authors proposed some cellular pathways that could be involved, such as Fas and growth factors signaling) would be necessary to understand the mechanism that leads oral GSH administration to ameliorate mucosal atrophy in the jejunum. 2. For analysis of Ggt1 and Gapdh mRNAs a real-time RT-PCR must be performed. Amplification by conventional PCR does not assure to be in the linear phase of the reaction and then it is not accurate. MINOR POINTS 1. In the text, it should be avoided to refer treatments as "50 GSH" or "500 GSH". It would be better to write "50 mg/kg GSH" or "500 mg/kg GSH". This is particularly important in the abstract, where the groups are not defined (and named). 2. In the abstract, it is mentioned: "both GSH concentration and Ggt1 mRNA expression decreases in the jejunum were also attenuated in rats following oral administration of GSH during fasting as compared with fasting alone". This is not correct. The decrease in GSH concentration it is not attenuated and a further decrease is reported. Ggt1 mRNA levels are increased (not decreased) after fasting, although attenuated with oral GSH. It should be changed. 3. Values shown in the abstract must have mean ± SEM 4. In the introduction, the sentences "In addition, these fasting states are also accompanied by a depletion of the critical antioxidant glutathione (GSH), which functions to eliminate induced ROS in the intestinal mucosa" and "Intestinal mucosal antioxidants such as GSH in particular provide critical protection against oxidative tissue injury by ROS that are present in the intestinal mucosa" are repetitive. 5. Some figures could be reassembled. Figures 7 and 8 and Table 1 are showing the same data.