

## PEER-REVIEW REPORT

**Name of journal:** World Journal of Gastrointestinal Pathophysiology

**Manuscript NO:** 33241

**Title:** Pharmacological inhibition of DGAT1 and insights into postprandial gut peptide secretion

**Reviewer's code:** 00495228

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

**Date sent for review:** 2017-06-14

**Date reviewed:** 2017-06-23

| 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 checked="" 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 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"/> No         | <input checked="" type="checkbox"/> Minor revision     |
| <input type="checkbox"/> Grade E: Poor                 |   | BPG Search:                                    | <input type="checkbox"/> Major revision                |
|  |   | <input type="checkbox"/> The same title        |  |
|  |   | <input type="checkbox"/> Duplicate publication |  |
|  |   | <input type="checkbox"/> Plagiarism            |  |
|  |   | <input checked="" type="checkbox"/> No         |  |

## COMMENTS TO AUTHORS

In the manuscript entitled "Pharmacological inhibition of DGAT1 and insights into postprandial gut peptide secretion" Maciejewski et al. described the effects of the pharmacological DGAT1 inhibitor on release of gut hormones. The manuscript confirms the previous published reports demonstrating that inhibition of the DGAT1 enzyme increases secretion of GLP-1 and PYY via augmented delivery of lipids to the distal portion of the gut where enteroendocrine L-cells are located. The experimental work presented in the manuscript is well designed and of good quality. The data are presented in the logical manner. However, there are some minor issues with data presentation and interpretation. 1. The Abstract is hard to read. It is too long and contained very detailed summary of the experimental data repeating the results section. Trimming down the size of the abstract and leaving out the exact values for the plasma gut peptide concentrations would help reading the abstract. 2. Fig. 1 does not show error bars in any of the presented graphs. This needs to be fixed. Did authors test the



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DGAT1 inhibitor in the DGAT1 knockout mice and what was the effect of the compound on GLP-1 secretion in the knockouts? 3. In Figs. 2-5 the vehicle group symbols and lines are very light and difficult to see in the printed version of the manuscript. The tone of the symbols needs to be adjusted. 4. Authors write that combination of the DGAT1 and DPPIV inhibitors leads to synergy and increased secretion of PYY (Abstract and main body of manuscript, pages 2, 11, 13 and 15). This is incorrect statement. Combo treatment versus DGAT1 inhibitor treatment produces somewhat lower PYY secretion (Fig. 3e,f). This needs to be corrected. Was the decrease in PYY secretion by the combo therapy significant when compared to the DGAT1 effect? 5. On page 12 authors write that effects of DGAT1 inhibitor is partially dependent on GPR119 activation, whereas on page 15 it is claimed that effects of DGAT1 inhibitor are GPR119 independent. Authors need to be consistent in their conclusions.

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**Name of journal:** World Journal of Gastrointestinal Pathophysiology

**Manuscript NO:** 33241

**Title:** Pharmacological inhibition of DGAT1 and insights into postprandial gut peptide secretion

**Reviewer's code:** 01427317

**Reviewer's country:** United States

**Science editor:** Fang-Fang Ji

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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 type="checkbox"/> Grade B: Minor language polishing           | <input type="checkbox"/> The same title        | <input type="checkbox"/> High priority for publication |
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| <input type="checkbox"/> Grade D: Fair      | <input type="checkbox"/> Grade D: Rejected                           | <input 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

The authors studied the effects of a DGAT1 inhibitor (PF-04620110; PF) and DGAT1 deficiency on corn oil-induced release of GLP-1 and PYY from L cells, and GIP from K cells. They clearly demonstrated that DGAT1 inhibition or deficiency enhanced the release of GLP-1 and PYY, but decreased GIP release. Combination of DGAT1 inhibition with a DPPIV inhibitor enhanced active GLP-1 levels, but had no effect on total GLP-1, PYY and GIP release. A lipase inhibitor Orlistat inhibited DGAT1 inhibition-induced changes. GPR119 knockout likely inhibited DGAT1 inhibition-induced active and total GLP-1 release. Overall data are clearly demonstrated and clinically worthy. However, some interpretations should be clarified and exact relation between DGAT1 inhibition and hormone release is still unclear; target cells (enterocytes and/or enteroendocrine cells); site of action (luminal, intracellular or basolateral); segmental responses (proximal or distal small intestine, or colon). 1. Since DGAT1 is expressed in enterocytes and DGAT1 inhibition decreases enterocyte TG synthesis, long-chain fatty acids LCFA

transport (absorption into enterocytes from the lumen and/or extrusion from the cells to subepithelial spaces) might be affected. Localization of nutrient receptors (GPCRs) on the enteroendocrine cells is still controversial; apical versus basolateral expression. Therefore, luminal nutrients likely activate apical GPCRs, but also may activate basolateral GPCRs after nutrient transport (absorption) through enterocytes. One possibility of the effects of DGAT1 inhibition on hormone release is that decreased LCFA absorption by inhibition of TG synthesis may increase luminal LCFA/monoacylglycerol (MG) content that activates apical LCFA/MG receptors (GPR40/120 and GPR119, etc) on enteroendocrine cells, then increase hormone release. Other is that increased LCFA/MG transport to subepithelial spaces by simple diffusion or intercellular pathway rather than TG transport as chylomicron formed in the enterocytes, may activate basolateral LCFA/MG receptors of endocrine cells, then increase hormone release. Orlistat experiment was excellent, but only showed that Orlistat decreased luminal LCFA/MG content, resulting in decreased LCFA/MG absorption (apical entry) into the enterocytes, rather than showing intracellular mechanisms as the authors stated. Since Orlistat abolished the effects of DGAT1 inhibition, TG degradation into LCFA and MG is likely upstream of the effects of DGAT1 inhibition. Please re-write the corresponding Results and Discussion. 2. Segmental effects; GIP containing K cells are predominantly located in the duodenum, whereas GLP-1 containing L cells are mainly present in the jejunum and ileum, and PYY is in the ileum. Major segment for lipid absorption is jejunum. Therefore, the rapid GIP release (peak at 1hr after corn oil challenge) is consistent with the duodenal response to luminal lipid. Inhibition of GIP release by Orlistat and GPR119 KO suggests that luminal LCFA/MG released by lipase in the duodenum stimulates GPR119 on the apical membrane of K cells. DGAT1 inhibition decreased GIP release, suggesting that PF may act as a GPR119 inhibitor, may accelerate duodenal transit time, then inhibit lipid exposure to duodenal K cells, or DGAT1 in K cells may act as signals to release GIP. Although PF delays gastric emptying, the accelerated intestinal transit may account for the delayed, but enhanced release of active GLP-1 (peak at 2 hr by PF, compared to peak at 1 hr by vehicle), since GLP-1 is present in the jejunum and ileum. PYY release reached to peak at 6 hr, further suggesting that more LCFA/MG reached to the ileal lumen, where PYY is more abundant. Please re-write the discussion in p14 the first and second paragraphs, accordingly. 3. Interpretation of GPR119 KO study is weird. Fig. 5 represents that active GLP-1 release enhanced by PF was abolished in GPR119 KO, total GLP-1 release enhanced by PF was reduced in KO (although total GLP-1 release stimulated by corn oil was reduced in KO), PYY release enhanced by PF was likely reduced in KO, and GIP release stimulated by corn oil was abolished in KO. Therefore, it seems that PF-induced enhanced GLP-1 and PYY release is GPR119 'dependent'. Please re-write the corresponding paragraphs (p13 the second paragraph, p15 the third paragraph), or discuss why the authors concluded GPR119 'independent'. Minor 1.



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Introduction, p6, line 9-10, 'the pattern of enterocyte secretion of gut hormones' should be 'enteroendocrine cell secretion'. 2. Results, p10-11, Figure 2E, 2F for PF and Sitagliptin study should be Figure 3E and 3F.