Reviewer's report

Title: Nrf2-mediated heme oxygenase-1 induction of PPI confers adaptive survival response to NSAID-induced gastric damages

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Reviewer: Young-Joon Surh

Reviewer's report:

This manuscript describes the induction of the stress-responsive enzyme heme oxygenase-1 (HO-1) by the proton pump inhibitor pantoprazole through activation of Nrf2. In an in vitro cell culture study, pantoprazole induced activation of Nrf2 as evidenced by increased nuclear translocation and subsequent ARE binding of this transcription factor. The typical NSAID, indomethacin enhanced the transcription of some proinflammatory and adhesion genes, which was suppressed by pantoprazole. In an in vivo animal gastritis model, patoprazole protected against indomethacin-induced gastric erosion, which was attenuated by the pharmacologic HO-1 inhibitor. Overall, the finding are interesting and provide the novel protective effects of proton pump inhibitors against NASAIDs-induced gastric damage. There are several issues that should be incorporated into the manuscript for the better revision.

1. Abstract, line 4: its acid suppressive action is not suffice to explain # its acid suppressive action does not suffice to explain.

2. The role of Nrf2 and HO-1 in adaptive stress response need to be briefly mentioned in a Background or Method session of the abstract.

3. page 1, line 3 from the bottom: HO-1 ... inductions after pantoprazole were significantly associated with the increased expressions of ... The underlined words are used in a singular noun. The corresponding verb (were) also needs to be corrected accordingly. Same correction need for the first line, p. 3 (expressions # expression) and many other locations throughout the text.

4. p. 2, line 4: .. because HO-1 inhibitor abolished these changes. In vivo mice model of ... # .. because a HO-1 inhibitor abolished these changes An in vivo mice model of... Numerous grammatical corrections are needed elsewhere (Introduction, Material & Methods, Results and Discussion parts).

5. keap1 should be abbreviated as Keap1 (capital for the first letter).

6. There is large standard deviation in the mRNA expression of HO-1 shown in Fig. 1A histogram. The average induction is less than 2 fold. In this respect, it would be better not to include the mRNA data as Western blot data alone clearly support the HO-1 induction by pantoprazole.
7. The number and the concentration unit should be apart (e.g., 300uM # 300 uM)

8. p. 8, line 15 & 16: As seen in Figure 2D, 3 uM pantoprazole exerted clear scavenging action of DMPO-adduct-generating hydroxyl radicals. This concentration of the compound is not the one used in the experiment

9. p. 8, line 19-21: These chemical results drawn from ESR were further validated with biological test using DCF-DA fluorescence measurement, showing that pantoprazole showed significant DCF-DA reduction in a dose dependent manner (p<0.05, Figure 2B). Fig 2B does not reflect the statement in this sentence. The ROS scavenging activity of pantoprazole may not be associated with its anti-inflammatory and gastroprotective effects against indomethacine and the EPR data does not necessarily be included in the manuscript. If the authors would like to relate the antioxidant effects of this PPI inhibitor with its protective effects on indomethacin-induced inflammation, a series of experiments using a conventional antioxidant will be necessary.

10. The manuscript title: Nrf2-mediated heme oxygenase-1 induction of PPI confers adaptive survival response to NSAID-induced gastric damages

The title is rather general and does not properly reflect the work the authors conducted. As the authors used indomethacin as a typical NASID and pantoprazole as a representative PPI inhibitor, the title should specify the names of compounds used. In addition, the majority of data are derived from in vitro cell culture studies. The suggested title would be:

title: A possible involvement of Nrf2-mediated heme oxygenase-1 upregulation in protective effect of the proton pump inhibitor pentoprazole against indomethacin-induced gastric damage in rats

11. While scientifically sound, the manuscript needs editorial and grammatical improvement.