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: Kazuhide Higuchi

Reviewer's report:

The author reported that pantoprazole can protect stomach against NSAIDs-induced damages by not only acid suppression but also Nrf2-driven HO-1 induction which occurs the improvement of NSAIDs-induced ischemia, attenuation of adhesion molecule, and decreasing inflammatory mediators. This study is interest. In vitro angiogenesis assay, the author reported that pantoprazole increase expression of angiogenic factors and activate NSAIDs-induced angiogenesis. However, there are some problems.

Comments to the author

Major

(1) The author reported that pantoprazole improve NSAIDs-induced ischemia. However, in this study, although pantoprazole increase expression of angiogenic factors and activate NSAIDs-induced angiogenesis, it is not enough persuasive to conclude that pantoprazole improve the ischemia. The authors should discuss about this point.

(2) In Figure2A, the author demonstrated that Western blots for either cytosolic keap1 or nuclear Nfr2 in a different time in the presence of 300 M pantoprazole. However, the author did not describe whether the lower concentration of pantoprazole could increase cytosolic keap1 and nuclear Nfr2 or not.

(3) Figure4 and Figure5 showed that indomethacin alone did not increase the expression of HO-1. However, indomethacin induced inflammation. Some reports found that indomethacin increased the expression of HO-1. The authors should discuss about this point.

(4) Figure4 and Figure5 showed that ZnPP# decreased the expression of HO-1. I think that ZnPP# inhibit only activity of HO-1. Can ZnPP# decrease the expression of HO-1?

(5) Figure3C showed that pantoprazole increased the expression of HIF-1. However, Figure5 showed that pantoprazole decreased HIF-1-#-DNA binding. It seems contradictory.

(6) The authors think all PPIs may induce HO-1 from the discussion. However, Yoda et al. (J Physiol Pharmacol. 2010 Jun;61(3):287-94) reported that lansoprazole, but not omeprazole, induced HO-1. The authors should refer this paper and discuss about this point.
Minor

(1) There is Figure 2E which show the change of DCF-DA fluorescence after different dosing of pantoprazole. However, in Figure legend, there is no description of Figure 2E. Is Figure 2E the part of Figure 2D?

(2) In p.8 l.23, the author described “PPI also increased expression of VEGF, mRNA and protein levels(Figure 2A) in RGM-1 gastric mucosal cells.” However, not Figure 2A but Figure 3A showed the expression of VEGF.

(3) In p.9 l.16-18, the author described “Additionally indomethacin challenge significantly increased the expressions of NADPH oxidase-1(NOX-1) as seen in Fig.4B”. However, Weston blotting of NOX-1 is shown in Figure 4A.

(4) In p.10 l.16, the author described “ICAL-1”. Is it mistake?

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.