

## Chloride Channels and Cytoprotection in Gastrointestinal Cells

Hideki Sakai, Akira Ikari and Noriaki Takeguchi

*Faculty of Pharmaceutical Sciences, Toyama Medical and Pharmaceutical University*

### Summary

Prostaglandin E<sub>2</sub> (PGE<sub>2</sub>) is known to have cytoprotective role on the gastric parietal cells against ethanol, but its mechanism is unknown. We recently found that PGE<sub>2</sub> opened a housekeeping chloride (Cl<sup>-</sup>) channel in the basolateral membrane of rabbit gastric parietal cells. This channel is sensitive to NPPB, a Cl<sup>-</sup> channel blocker. In the present study, we investigated the cellular signaling mechanism of PGE<sub>2</sub>-induced activation of the NPPB-sensitive Cl<sup>-</sup> channel and cytoprotective function of the channel by patch-clamp technique, Fura 2-fluorescence measurement and enzyme immunoassay. Ca<sup>2+</sup>, nitric oxide (NO) and cGMP were involved as intracellular messengers in the PGE<sub>2</sub>-induced activation of the channel. A novel bi-functional prostaglandin EP3 agonist/EP1 antagonist, ONO-NT-012, also increased both the [Ca<sup>2+</sup>]<sub>i</sub> and the channel opening. The PGE<sub>2</sub>-induced effects were blocked when parietal cells were pre-treated with pertussis toxin (PTX). Our results indicate that PGE<sub>2</sub> elicits the EP3 receptor-mediated increase in the [Ca<sup>2+</sup>]<sub>i</sub> via a PTX-sensitive GTP-binding protein, resulting in successive production of NO and cGMP, and the opening of the housekeeping Cl<sup>-</sup> channel. On the other hand, nitroprusside, a NO donor, and dibutyryl cGMP showed cytoprotective effect on the BCECF-loaded isolated parietal cell against ethanol. The cytoprotective effect of dibutyryl cGMP was abolished when the Cl<sup>-</sup> channel was inhibited by NPPB. We suggest that the PGE<sub>2</sub>-elicited cytoprotection was mediated via mobilization of the NO/cGMP pathway and that the target was a housekeeping Cl<sup>-</sup> channel in the basolateral membrane of the parietal cell. The cytoprotective action of PGE<sub>2</sub> is mediated, at least, in part via stabilization of the membrane potential