The role of protease-activated receptors in regulating other ion channels

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The authors of a recent review article on the main ion channels and receptors associated with visceral hypersensitivity in irritable bowel syndrome (IBS) emphasized the key role of protease-activated receptors (PAR)-2 in visceral hyperalgesia [1]. For the understanding of symptoms of IBS, it is fundamental to understand the interaction of ion channels systems: PAR-2 has been shown to potentiate transient receptor potential vanilloid (TRPV) 1 activation through protein kinase (PK) C- and PKA-dependent mechanisms. This involves translocation of these PKs to the plasma membrane and phosphorylation of TRPV1 as demonstrated for dorsal root ganglia cells. Inhibition of PKC in rats in vivo inhibited the hyperalgesic response to PAR-2 agonists and capsaicin, the TRPV1 stimulator [2]. Another interaction of ion channels, which may help understand the symptom of diarrhea if it is not related to increased peristalsis in a variant of IBS, has become evident from more recent experiments in an intestinal epithelial cell line mounted in Ussing chambers. It was revealed that basolateral PAR-2 activation induces cystic fibrosis transmembrane-conductance regulator (CFTR)-mediated chloride secretion by prostaglandin (PG) E2 confirming the general applicability of this mechanism, previously thought to be the likely explanation for PGE2- and PGF1-mediated stimulation of chloride secretion by PAR-2 activation [3]. The interaction with CFTR may explain changes in bowel habit by inducing the diarrhea phenotype of IBS because chloride secretion is a key event in the pathogenesis of secretory diarrhea through reduction in the osmotic gradient across intestinal epithelial cells.

Consequently, therapeutic studies are warranted to explore PKC and PG inhibitors in the treatment of IBS-related symptoms.

References

1. de Carvalho Rocha HA, Dantas BP, Rolim TL, Costa BA, de Medeiros AC. Main ion channels and receptors associated with visceral hypersensitivity in irritable bowel syndrome. *Ann Gastroenterol* 2014;27:200-206.
3. van der Merwe JQ, Ohland CL, Hirota CL, MacNaughton WK. Prostaglandin E2 derived from cyclooxygenases 1 and 2 mediates intestinal epithelial ion transport stimulated by the activation of protease-activated receptor 2. *J Pharmacol Exp Ther* 2009;329:747-752.

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