Abstract:

Protease-activated receptors (PARs) are expressed in the enteric nervous system. Excessive release of proteases has been reported in functional and inflammatory bowel diseases. Studies in several animal models indicate the involvement of neural PARs. We studied the actions of different PAR-activating peptides (AP) in the human submucous plexus and performed comparative studies in guinea pig submucous neurons. We used voltage- and calcium-sensitive dye recordings to study the effects of PAR1-AP, PAR2-AP, PAR4-AP, the PAR1 activator thrombin, and the PAR2 activator tryptase on neurons and glia in human and guinea pig submucous plexus. Human preparations were derived from surgical resections. Levels of mucosal secretion evoked by PAR-APs were measured in Ussing chambers. PAR1-AP and thrombin evoked a prominent spike discharge and intracellular Ca(2+) concentration ([Ca](i)) transients in most human submucous neurons and glia. PAR2-AP, tryptase, and PAR4-AP caused significantly weaker responses in a minor population. In contrast, PAR2-AP evoked much stronger responses in enteric neurons and glia of guinea pigs than did PAR1-AP or PAR4-AP. PAR1-AP, but not PAR2-AP or PAR4-AP, evoked a nerve-mediated secretion in human epithelium. The PAR1 antagonist SCH79797 inhibited the PAR1-AP, and thrombin evoked responses on...
neurons, glia, and epithelial secretion. In the submucous layer of human intestine, but not guinea pig intestine, PAR2-AP evoked [Ca][i] signals in CD68(+) macrophages. In the human submucous plexus, PAR1, rather than PAR2 or PAR4, activates nerves and glia. These findings indicate that PAR1 should be the focus of future studies on neural PAR-mediated actions in the human intestine; PAR1 might be developed as a therapeutic target for gastrointestinal disorders associated with increased levels of proteases.