Abstract:

Background H(2) S actions in the gut involve neural activation. This study aimed to reveal the signaling mechanisms responsible for the pro-secretory effect of H(2) S by using TRPV1 and unselective TRP blockers and inhibitors of other signaling cascades hitherto described to be targeted by H(2) S elsewhere.

Methods Using chamber voltage clamp technique was used to study actions of the H(2) S donor NaHS on secretion in guinea-pig and human colon. NaHS effects on guinea-pig primary afferents were also evaluated.

Key Results NaHS evoked secretion was significantly reduced in guinea-pig and human tissue by the selective TRPV1 blockers capsazepine, AMG9801, SB705498, BCTC; LY294002 (Phosphatidylinositol-3 kinase (PI3K) inhibitor), SKF96365 (store operated calcium channel blocker), 2-APB (inositol triphosphate blocker), and atropine but not by HC030031 (TRPA1 blocker) or L- and T-type calcium channel antagonists.

Actions of TRPV1 antagonists suggested non-competitive inhibition at multiple sites. In guinea-pig colon, Gd(3+) and La(3+) (unselective TRP blockers) had no effects while ruthenium red reduced NaHS effects; in human colon Gd(3+) attenuated NaHS response. NaHS response was inhibited by neurokinin-1 and -3 receptor blockers in guinea-pig and neurokinin-1 and -2 receptor blockade in human tissue. There was cross-desensitization between NaHS
and capsaicin responses. NaHS induced capsazepine and LY294002 sensitive afferent discharge.

Conclusions & Inferences H(2) S evokes mucosal secretion by targeting TRPV1 expressing afferent nerves which activate cholinergic secretomotor neurons via release of substance P acting in a species dependent manner on neurokinin-1, -2 or -3 receptors. Besides TRPV1 signaling H(2) S may target intracellular calcium dependent pathways and PI3K.