Impact of endogenous hydrogen sulfide on somatic and visceral pain signals

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Hydrogen sulfide (H_2S), a toxic gas, is formed from L-cysteine by enzymes including cystathionine-γ-lyase (CSE) in the mammalian body, and is now considered the third gasotransmitter after nitric oxide and carbon monoxide. Although ATP-sensitive K^+ (K_{ATP}) channels were first identified as target molecules for H_2S, it is now known that H_2S targets multiple molecules other than K_{ATP} channels. A series of our studies have shown that H_2S enhances T-type Ca^{2+} channel-dependent membrane currents, and that H_2S causes sensitization/activation of nociceptors in a manner dependent on $Ca_v3.2$ among three isoforms of T-type Ca^{2+} channels, leading to peripheral hyperalgesia. Interestingly, the acceleration of $Ca_v3.2$ signaling by CSE-derived endogenous H_2S is involved in the maintenance of neuropathic pain caused by surgical spinal nerve injury or by repeated administration of paclitaxel, an anti-cancer agent. The sensitization/activation of $Ca_v3.2$ by H_2S in the peripheral ending of nociceptors also participates in signaling of visceral pain in distinct organs including the pancreas, colon and bladder. Of interest is that the visceral pain accompanying pancreatitis and cystitis involves the upregulation of CSE and subsequent increase in endogenous H_2S generation. Together, our studies on the roles of the CSE/H_2S/$Ca_v3.2$ cascade in pain signaling shed light on the pathogenesis of neuropathic and visceral pain, and may open a new frontier in clinical pain management.