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Repagermanium attenuates H_2S-induced acceleration of $Ca_v3.2$ T-type calcium channel activity and pain sensitivity by directly interacting with H_2S

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Repagermanium, once hydrolyzed into THGP (3-(trihydroxygermyl)propanoic acid) in an aqueous solution, exhibits various biological activities and attenuates osteoporosis, pain, inflammation, etc., although the underlying molecular mechanisms remain unclear. The present study was conducted to see whether THGP would directly interact with H_2S, a gasotransmitter, generated by some enzymes including cystathionine-γ-lyase (CSE), which promotes pain sensation by increasing $Ca_v3.2$ T-type calcium channel (T-channel) activity. ^{1}H-NMR and LC-MS/MS spectrum analyses indicated that THGP reacts with SH^- derived from H_2S donors, NaSH or Na_2S, generating a sulfur-containing compound. In $Ca_v3.2$-transfected HEK293 cells, THGP abolished Na_2S-induced enhancement of T-currents. In mice, THGP suppressed the mechanical allodynia caused by intraplantar Na_2S or burn injury, as assessed by von Frey test, as did a T-channel blocker and CSE inhibitor. Western blotting demonstrated the burn injury-induced upregulation of CSE protein in the plantar skin. These data suggest that THGP directly interacts with H_2S, thereby attenuating H_2S-dependent enhancement of $Ca_v3.2$ activity and pain sensitivity. The burn injury-induced allodynia is considered to involve the CSE upregulation followed by acceleration of the $H_2S/Ca_v3.2$ pathway.

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