Repagermanium attenuates H₂S-induced acceleration of Ca_v3.2 T-type calcium channel activity and pain sensitivity by directly interacting with H₂S

Nene Koike¹, Kaho Sugimoto¹, Hiroshi Masuda¹, Yasuhiro Shimada², Katsuyuki Sato², Takashi Nakamura², Hiroaki Yamaguchi³, Genzou Tanabe⁴, Shinsuke Marumoto⁵, Yoshihito Kasanami¹, Fumiko Sekiguchi¹, Tsuyako Ohkubo⁶, Shigeru Yoshida⁷, Atsufumi Kawabata¹

¹Lab. Pharmacol. Pathophysiol., Fac. Pharm., Kindai Univ., ²Asai Germanium Res Inst., ³Yamagata Univ. Grad. Sch. Med. Sci., ⁴Lab. Org. Chem., Fac. Pharm., Kindai Univ., ⁵Joint Res. Cent., Kindai Univ., ⁶Div. Basic Med. Sci. Fund. Nurs., Fac. Nurs., Fukuoka Nurs. College, ⁷Dep. Life Sci. Engineer., Kindai Univ.

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 H₂S, 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. ¹H-NMR and LC-MS/MS spectrum analyses indicated that THGP reacts with SH⁻ derived from H₂S donors, NaSH or Na₂S, generating a sulfur-containing compound. In Ca_v3.2-transfected HEK293 cells, THGP abolished Na₂S-induced enhancement of T-currents. In mice, THGP suppressed the mechanical allodynia caused by intraplantar Na₂S 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 H₂S, thereby attenuating H₂S-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 H₂S/Ca_v3.2 pathway.