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Poster Sessions

Role of the cystathionine γ -lyase/H₂S pathway in paclitaxel-induced HMGB1 release from macrophages and its impact on the pathogenesis of peripheral neuropathy in mice

Itsuki Yamaguchi¹, Risa Domoto¹, Fumiko Sekiguchi¹, Maho Tsubota¹, Atsufumi Kawabata¹

¹*Lab. Pharmacol. Pathophysiol., Fac. Pharm., Kindai Univ.*

We have reported that inhibitors of cystathionine γ -lyase (CSE), an H₂S-generating enzyme, reverse paclitaxel (PCT)-induced peripheral neuropathy (PIPn) in rats (Neuroscience 2011;188:148-156), and that PIPn in rats and mice involves macrophage-derived HMGB1, a DAMP molecule (Neuropharmacology 2018;141:201-213). Thus, we investigated a possible crosstalk between CSE/H₂S and HMGB1 pathways in macrophages and its implication for PIPn in mice. Repetitive i.p. administration (days 0, 2, 4 and 6) of PCT caused mechanical allodynia, as assessed by von Frey test, which was prevented by repeated i.p. administration of DL-propargylglycine (PPG), a CSE inhibitor. A single administration of PPG as well as β -cyano-L-alanine (BCA), another CSE inhibitor, reversed the established PIPn. In macrophage-like RAW264.7 cells, PCT at 1 μ M produced HMGB1 release, an effect abolished by PPG or BCA. Na₂S, an H₂S donor, at 30-100 μ M also caused HMGB1 release from RAW264.7 cells, which was blocked by N-acetyl-L-cysteine, an antioxidant. Our data suggest that PCT-induced HMGB1 release from macrophages involves endogenous H₂S generated by CSE, contributing to PIPn in mice.