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Effect of tacrolimus on caerulein-induced pancreatitis-related pain in mice

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Transient receptor potential vanilloid-1 (TRPV1) expressed in nociceptors is directly phosphorylated and activated by protein kinase C, and involved in signaling of somatic and visceral nociception including pancreatic pain. On the other hand, $Ca_v3.2$ T-type Ca^{2+} channels expressed in nociceptors are functionally upregulated by phosphorylation with protein kinase A (1) and also participate in pancreatitis-related pain (2, 3). Calcineurin, a phosphatase, negatively regulates various channel functions including TRPV1, and calcineurin inhibitor-induced pain syndrome (CIPS) by tacrolimus (FK506), a calcineurin inhibitor, used as an immunosuppressant, has been a clinical problem. We thus examined and characterised the effect of tacrolimus on pancreatitis-related pain in mice.

Adult male ddY mice (n=6-8) were administered i.p. with caerulein (Cer) at 50 µg/kg at 1-h intervals, 6 times in total. FK506 at 10 mg/kg was administered i.p. 10 min or 24 h after the final dose of Cer. Referred hyperalgesia was evaluated 30 min after FK506 treatment with the von Frey test. SB366791 (SB), a TRPV1 inhibitor, at 500 µg/kg or NNC 55-0396 (NNC), a T-type Ca^{2+} channel blocker, at 10 mg/kg was administered i.p. 30 min before FK506 treatment.

Referred hyperalgesia accompanying pancreatitis occurred after 6 doses of Cer, and was not altered by FK506. The referred hyperalgesia disappeared 24 h after the final dose of Cer, but recurred when FK506 was administered (Fig. 1A). The facilitating effect of FK506 on pancreatitis-related pain was suppressed by SB (Fig. 1B), but not NNC.

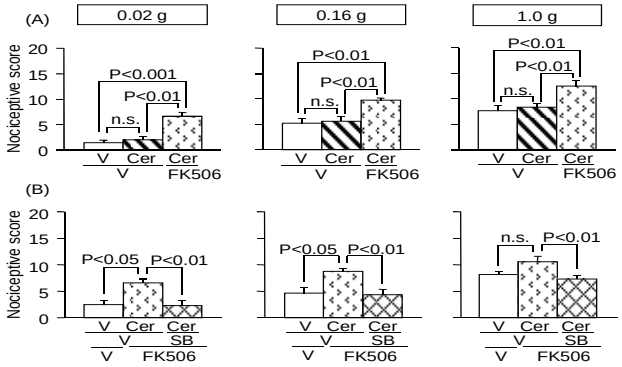

Fig. 1 (A) Recurrence by FK506 of the referred hyperalgesia accompanying pancreatitis 24 h after the final dose of Cer in mice. (B) Effect of SB on the FK506-

induced recurrence of the referred hyperalgesia 24 h after the final dose of Cer in the mice. n.s., not significant. (Kruskal-Wallis H test followed by LSD-type test)

In summary, tacrolimus, a calcineurin inhibitor, delays the disappearance of acute pancreatitis-related pain through facilitation of TRPV1 activity in mice with Cer-induced pancreatitis, suggesting that calcineurin negatively regulates pancreatic pain processing.

(1) Sekiguchi F et al. (2013) Br J Pharmacol 168: 734–745

(2) Nishimura S et al. (2009) Gut 58: 762-770

(3) Fukushima O et al. (2010) J Neurosci Res 88: 3198-3205