Novel PAC1 receptor antagonists alleviate paclitaxel-induced mechanical allodynia by inhibiting astrocytic activation

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Paclitaxel (PTX) is an anticancer agent mainly used as the primary therapy for malignancies such as ovarian, breast, and stomach cancers. However, it frequently induces severe peripheral neuropathy including mechanical allodynia, numbness in a stocking-glove distribution. Recently, we developed novel and small-molecule PACAP type 1 (PAC1) receptor antagonists named PA-8 and PA-81004. In the present study, we examined the effects of novel PAC1 antagonists on PTX-induced mechanical allodynia in mice.

Repeated administration of PTX (2 mg/kg, once a day for 5 days, i.p.) induced mechanical allodynia of the hind paw and activation of spinal astrocyte. Single intrathecal injection of PA-8 (1 nmol) suppressed both PTX-induced mechanical allodynia and astrocytic activation, suggesting that spinal astrocytes activated by PACAP/PAC1 receptor signaling are involved PTX-induced mechanical allodynia.

Next, we examined the systemic administration of the PAC1 receptor antagonists. Single oral administration of PA-8 or PA-81004 (3-30 mg/kg) dose-dependently alleviated PTX-induced mechanical allodynia. The effects of PA-81004 were more potent than PA-8. Repetitive treatment with PA-8 (30 mg/kg, p.o.) 30 minutes before PTX administration almost completely inhibited the induction of mechanical allodynia. These results suggest that PA-8 exerts both therapeutic and preventive effects. Our novel PAC1 receptor antagonists may become orally available analgesics against PTX-induced peripheral neuropathy.