Novel small-molecule antagonist of PAC1 receptor ameliorates nitroglycerin-induced migraine-related behaviors in mice

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Migraine is neurological disorder that includes unilateral headache. Although migraine is highly prevalent, its pathophysiology is unclear. In humans, intravenous administration of pituitary adenylate cyclase-activating polypeptide (PACAP), but not vasoactive intestinal polypeptide (VIP), induces migraine-like attacks, suggesting that selective PACAP type 1 (PAC1) receptor antagonist could be a new anti-migraine drug. Previously, we have developed novel small-molecule antagonists of the PAC1 receptor. In the present study, we investigated the effect of PA-8, one of novel PAC1 receptor antagonist, on pain-related behaviors induced by nitroglycerin (NTG) which is widely studied and accepted as an animal model of migraine.

Single or repeated administration of NTG (5 mg/kg, i.p.) induced transient and long-lasting mechanical allodynia of the hind paw, respectively. NTG also induced the increase in the number of c-fos-positive cells in the trigeminal nucleus caudalis (TNC), light-aversive behavior, and anxiety-like behavior in mice. Single or repeated administration of PA-8 (10-30 mg/kg, i.p.) reduced NTG-induced mechanical allodynia, the number of c-fos-positive cells, and anxiety-like behavior. Single administration of PA-8 (30 mg/kg, i.p.) had a tendency to reduce the light-aversive behavior induced by NTG.

The present results suggest that PAC1 receptor is deeply involved in the NTG-induced migraine-related aversive responses and that PAC1 receptor antagonists may become novel anti-migraine drug.