Migraine is a common neurovascular disorder with uncomplete understood pathogenetic mechanisms. Pain modulation is an important issue in migraine research field. Therefore, understanding the pathogenesis of migraine and developing new treatments based on pathophysiological mechanisms are major issues in neuropharmacology.

It has been reported that administration of pituitary adenylate cyclase-activating polypeptide (PACAP) induces migraine-like headache in humans, suggesting that PACAP plays an important role in the activation of trigeminal system and migraine pain. On the other hand, vasoactive intestinal polypeptide (VIP) induce only a minimal and short-lasting headache in both healthy volunteers and migraine patient. Given clinical experiments that PACAP but not VIP elicits a migraine-like attack, PAC1 receptors are implicated in the migraine pathophysiology, and that selective PAC1 receptor antagonist could be a new anti-migraine drug.

Although several PAC1 antagonists such as PACAP 6-38 have been reported, all of them are peptide compounds. Recently, we have developed a novel small-molecule antagonist of the PAC1 receptor named PA-8 by in silico screening and in vitro pharmacological assays. Moreover, we synthesized novel PA-8-derivative compounds named PA-810 and 81004. In the present study, we investigated the effects of PA-8 and its derivative compounds on pain-related behaviors induced by nitroglycerin (NTG) which is widely studied and accepted as animal model of migraine.

Single and repeated (once a day for three days) administration of NTG (5 mg/kg, i.p.) in mice induced transient and long-lasting mechanical alldynia of the hind paw, respectively. Single pretreatment PA-8, 810, or 81004 (10-30 mg/kg, i.p.) inhibited the induction of NTG-induced transient mechanical alldynia. Repeated administration PA-8, 810, or 81004 (10 mg/kg) also inhibited the induction of long-lasting mechanical alldynia induced by NTG administration.

These results suggest that PAC1 receptor is deeply involved in the NTG-induced pain and that PAC1 receptor antagonists may be a novel anti-migraine drug.