Effects of newly developed small-molecule PACAP type 1 receptor antagonists on itch-like behaviors in mice.

Ichiro Takasaki[1], Ryuta Ikeda[1], Mayuko Murata[1], Sho Kato[1], Takuya Okada[2], Naoki Toyooka[2], Hiroaki Gouda[3], Atsuro Miyata[4], Takashi Kurihara[4]

[1]Dept. Pharmacol., Grad. Sch. Sci. Eng., Univ. Toyama, [2]Dept. Bio-func. Mol. Eng., Grad. Sch. Sci. Eng., Univ. Toyama, [3]Dept. Analytical and Physical Chem., Sch. Pharmacy, [4]Dept. Pharmacol., Grad. Sch. Med. Dent., Kagoshima Univ.

The role of pituitary adenylate cyclase-activating polypeptide (PACAP) in pain transmission has been well documented, but its involvement in itch transmission is entirely unclear. We recently developed novel small-molecule antagonists of PACAP type 1 (PAC1) receptor including PA-8 by *in silico* screening. In this study, using PA-8, we investigated the possible involvement of PACAP/PAC1 receptor signaling in itch.

Both intradermal (i.d.) and intrathecal (i.t.) injection of PACAP (1 pmol–1 nmol) dose-dependently elicited scratching/biting behaviors, and these behaviors were inhibited by subcutaneous pretreatment with the μ-opioid receptor antagonist naltrexone (1 mg/kg). The scratching/biting behaviors induced by i.d. and i.t. PACAP were inhibited by i.d. and i.t. co-injection of PA-8 (0.1–10 nmol), respectively. The application of 5-HT (200 nmol in EtOH) to the skin elicited scratching behaviors, and they were suppressed by i.t., but not i.d., pretreatment of PA-8 (0.1–10 nmol). Next, we examine the effects of PA-8 on pruritic models. In the itch model induced by cutaneous application of acetone/ether and water (AEW, a dry skin model) or 2,4-dinitrofluorobenzene (DNFB, an atopic dermatitis model), single oral administration of PA-8 (3 – 30 mg/kg) dose-dependently suppressed the itch-associated behaviors.

These results suggest that PACAP/PAC1 receptor signaling in the skin and/or spinal cord is involved in an itch sensation. The small-molecule PAC1 receptor antagonist may become an orally available antipruritic drug in the treatment of acute and chronic itch.