Analysis of oxytocin as a positive allosteric modulator（PAM）of the opioid δ- and κ-receptors.

Yuki Yoshida[1], Hideki Takahashi[2,3], Haruka Ono[2,3], Yoshiyuki Meguro[2,4], Miyano Kanako[2], Miki Nonaka[2], Shigeto Hirayama[2,3], Takaaki Mizuguchi[3], Masaki Kobayashi[1], Ryoma Tagawa[1], Hideaki Fuji[3], Yoshikazu Higami[1], Yasuhito Uezono[2,5,6]

[1]Lab. Mol. Patho & Metab., Grad. Pharmaceu., Tokyo Univ Sci., [2]Div. Cancer Pathophysiol., NCCRI., [3]Lab. Med. Chem., Kitasato Univ. Sch. Pharmacy., [4]Dept. Surg., Jichi Med. Univ., Sch. Med., [5]Div. Suppo. Care Res., EPOC, NCC., [6]Cent. Suppo. Care., NCCH.

Oxytocin (OT), composed of nine amino acids, has a wide range of physiological functions such as uterine contractions, maternal/social behavior and anti-stress effects. Recently, it has been reported that OT released from parvocellular neurons alleviates pain. Analgesic effects of OT might be involved in the μ- and κ-opioid receptors (OR) in the rats because it was partially inhibited by the antagonists of μ- and κ-ORs but not δ-ORs. However, it has not been elucidated the mechanism in detail. While we previously reported that OT could enhance the μ-OR activity as a positive allosteric modulator (PAM), it remains unclear whether OT behaves as a PAM for the δ- and κ-OR. We therefore analyzed activities of δ- and κ-OR stimulated by OT in two types of HEK293 cells stably expressing δ- and κ-OR, respectively. For the measurement, we used the CellKey™ assay system that measures changes of impedance following OR activation. In the assay, OT failed to exert agonistic effects on the δ- and κ-OR, whereas it enhanced the κ-OR activity induced by κ-OR agonists dynorphin A, U50488 and morphine. Interestingly, OT at 10^{-6} M had no effect on the δ-OR activity induced by δ-OR agonists Leu- and Met-enkephalin, SNC80 and morphine. We also revealed all amino acids of OT except Leu in the position 8 could be involved in PAM activity at the κ-OR. In addition, our competitive receptor-binding analysis disclosed that OT had no effect on the κ-OR orthosteric binding sites. Hence, OT could function as a κ-OR PAM in addition to a μ-OR PAM.