Antinociceptive effects of innovative nociceptin/orphanin FQ receptor agonists infused by intrathecal route in rats

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Severe pain occurs in the context of many diseases and conditions, including cancer, back pain, osteoarthritis, trauma, fibromyalgia, diabetic neuropathy, and migraine-related headache and is a leading cause of disability. Morphine, the natural alkaloid extracts from Papaverum Somniferum, is one of the most effective analgesic drugs used to relief severe pain. During long-term treatments, the high efficacy of mu-opioid receptor (MOP) agonists is influenced by the presence of side effects and the development of tolerance.

Recently, a novel opioid like receptor called nociceptin/orphanin FQ receptor (NOP) has been discovered. The NOP receptor shows high degree of homology with the classical opioid receptors but does not bind opioid ligands. Nociceptin/orphanin FQ (N/OFQ) is the endogenous peptide known to be a NOP selective agonist and consequently involved in pain modulation. Although N/OFQ response is complex, studies in animal models underline antinociceptive properties of this peptide following spinal administration. Moreover, the spinal co-administration of N/OFQ and morphine produces a synergistic analgesic response in non human primates (Ko et al, 2009).

Aim of this study was to characterize the analgesic profile of two new peptide NOP agonists, UFP-112 (full agonist) and UFP-113 (partial agonist), in the rat using the intrathecal route performed by spinal catheterization according to Yaksh & Rudy (1976) method. Acute intrathecal injection of UFP-112 induced antinociceptive response at lower dosages (0.03-1 nmol i.t.) compared to morphine (0.1-3 nmol i.t.) and similar to N/OFQ (0.01-3 nmol i.t.) efficacy in the rat paw pressure test. In the same test the NOP partial agonist UFP-113 was effective in a 0.001-1 nmol dose range after acute intrathecal injections. Osmotic pumps, connected with spinal intrathecal catheter, were used in order to characterize the antinociceptive profile of these compounds during continuous infusion. 0.1 nmol/h i.t. UFP-112 and UFP-113 continuous treatments showed a pain relief efficacy comparable to morphine and N/OFQ continuously infused at 3 nmol/h. The potent NOP agonists were not able to retard the development of tolerance with respect to N/OFQ. At the active doses these compounds, acutely or continuously administered, did not alter motor coordination (rota rod test). At last, compound cross tolerance was evaluaed. The acute intrathecal injection of morphine evoked analgesic effects in both groups tolerant to the full NOP agonists, N/OFQ and UFP-112. Neither morphine nor N/OFQ induced antinociceptive effects in morphine- and UFP-113-tolerant rats, suggesting that morphine and the NOP partial agonist UFP-113 did not electively bind to MOP and NOP receptors respectively.

In conclusion, the high potenty of these new compounds and ability to elicit antinociceptive effects after acute and chronic intrathecal administration is described. Based on the emerging antinociceptive activity of NOP stimulation, the possible relevance of bivalent MOP/NOP agonists is suggested in order to improve pain treatment.