In vitro pharmacological characterization of NiK-21273, a novel nociceptin/orphanin FQ receptor antagonist

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The purpose of the present study was to characterize the in vitro pharmacological profile of the novel nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor ligand NiK-21273 (2-[3-[4-(2-Chloro-6-fluoro-phenyl)-piperidin-1-ylmethyl]-2-(morpholine-4-carbonyl)-indol-1-yl]-acetamide). The effects of this molecule were assessed in calcium mobilization studies performed with cells expressing the human recombinant NOP or classical opioid receptors as well as in bioassay studies performed with isolated tissues expressing native NOP receptors.

Calcium mobilization studies were performed in cells expressing the receptor of interest and chimeric G proteins that forced the receptor to couple via the calcium pathway. N/OFQ (pEC_{50} of 9.19), dermorphin (8.26), dynorphin A (9.19), and DPDPE (8.36) produced concentration-dependent stimulatory effects in cells expressing the NOP, MOP, KOP and DOP receptors, respectively. Inhibition response experiments were performed with naloxone and NiK-21273 against a fixed concentration of agonist, approximately the EC_{80}. NiK-21273 was inactive against classical opioid receptor agonists while fully inhibiting the N/OFQ response at NOP with a pK_B of 7.38. In contrast, naloxone was inactive against N/OFQ while inhibiting the effects of opioid agonists with higher potency at MOP (pK_B of 8.73) than KOP (7.00) and DOP (6.80) receptors. In classical Schild analysis experiments, NiK-21273 produced a concentration-dependent and parallel rightward shift of the concentration-response curve to N/OFQ which was compatible with a surmountable type of antagonism. A pA_2 value of 7.77 was derived from these experiments.

NiK-21273 was also assessed in the electrically-stimulated mouse and rat vas deferens. In both preparations NiK-21273 did not modify per se the electrically induced twitch up to 1 µM. However, in the 10 nM - 1 µM range NiK-21273 produced a concentration dependent rightward shift of the concentration response curve to N/OFQ without significantly affecting the maximal agonist effect. Schild analysis of these data yielded a pA_2 value of 7.74 and 7.75 in the mouse and rat tissues, respectively. In addition 1 µM NiK-21273 did not modify the inhibitory effects exerted by DPDPE in the mouse vas deferens.

In conclusion the results of these studies demonstrated that NiK-21273 behaves in vitro as a pure, fairly potent, and highly selective NOP receptor antagonist. This molecule represents a novel and useful tool for investigating the physio-pathological role played by the N/OFQ - NOP receptor system.