EFFECT OF NOVEL NOCICEPTIN/ORPHANIN FQ–NOP RECEPTOR LIGANDS ON FOOD INTAKE IN WISTAR RATS

CIFANI CARLO[a], POLIDORI CARLO[a], CALÒ GIROLAMO[b], MASSI MAURIZIO[a]

[a]Department of Experimental Medicine and Public Health, University of Camerino, I-62032, Camerino, Italy
[b]Department of Experimental and Clinical Medicine, Section of Pharmacology and Neuroscience Center, University of Ferrara, I-44100 Ferrara, Italy

Activation of the NOP receptor by the endogenous ligand nociceptin/orphanin FQ (N/OFQ) stimulates feeding in freely feeding rats (2). The present study evaluated the effect of two newly synthesized peptidergic NOP receptor agonists and one NOP receptor antagonist on food intake.
[(pF)Phe^{4}Aib^{7}Arg^{14}Lys^{15}]N/OFQ-NH_2 (UFP-112) has been designed as a novel peptide ligand for the N/OFQ peptide receptor (NOP) (Calò, personal communication) by combining into the same peptide sequence several different chemical modifications previously reported to increase N/OFQ potency. In vitro data obtained in the electrically stimulated mouse vas deferens demonstrated that UFP-112 behaved as a full agonist at the NOP receptor displaying very high potency (pEC50 9.43). UFP-113 ([F/G(pF)Phe^{4}Aib^{7}Arg^{14}Lys^{15}]N/OFQ-NH_2) has been designed as a partial agonist at the NOP receptor (Calò, personal communication).
Freely feeding Wistar rats were injected into the brain lateral ventricle with the NOP receptor agonists UFP-112 (0.01, 0.03, 0.05 and 0.1 nmol/µl), UFP-113 (0.03, 0.05, 0.2, and 0.4 nmol/µl) alone or with the pre-treatment with NOP receptor antagonist UFP-101 ([Nphe^1,Arg^{14},Lys^{15}]N/OFQ NH_2) (7.4, 10 and 20 nmol/µl).
Results showed that UFP-112 produced, starting from the dose of 0.03 nmol/µl, a potent and far more pronounced hyperphagic effect than that of N/OFQ 4.2 nmol/µl. The partial agonist UFP-113 produced a significant increase in food intake starting from the dose of 0.05 nmol/µl. As already known the NOP receptor antagonist UFP-101 did not modify feeding in freely feeding rats (1). Tested at the dose of 20 nmol/µl, against UFP-112 (0.05 nmol/µl), it significantly reduced its hyperphagic effect, while it significantly reduced, at the dose of 10 nmol/µl the hyperphagic effect of UFP-113 (0.2 nmol/µl). The present findings indicate that UFP-112, UFP-113 may act as potent and long-lasting NOP receptor agonists. Overall, the results indicate that these compounds may represent valuable pharmacological tools to investigate the functional role of the brain N/OFQ system.

[1] Economidou D, Policani F, Angellotti T, Massi M, Terada T, Ciccocioppo R.. Peptides. 2006; 27:775-783

[2] Pomonis JD, Billington CJ, Levine AS. Neuroreport. 1996; 8:369-371.