THE EFFECTS OF UFP112, A NOVEL NOCICEPTIN/ORPHANIN FQ-NOP RECEPTOR LIGAND, ON COLONIC PROPULSION AND DEFECATION IN PHYSIOLOGICAL AND PATHOLOGICAL CONDITIONS

Broccardo M.[a], Agostini S.[a], Guerrini R.[b], Improta G.[a], Linari G.[a], Petrella C.[a]

[a] Dept. Human Physiology and Pharmacology, University of Rome “Sapienza”, [b] Dept. Pharmaceutical Sciences and Biotechnology Center, University of Ferrara - Italy

Nociceptin/orphanin FQ (N/OFQ) has been reported to affect gastrointestinal motor and secretory responses in various species. Recently, a novel N/OFQ analogue, [(pF)Phe^{4}Aib^{7}Arg^{14}Lys^{15}]N/OFQ-NH_2 (UFP_{112}), has been synthesized and demonstrated to behave as a highly potent agonist at N/OFQ receptor (NOP) and to produce long-lasting effects in vivo. The main purpose of this study was to further evaluated the pharmacological profile of UFP_{112} and to compare its effects with those of N/OFQ on normal distal colonic propulsion of a glass bead, on colonic propulsion stimulated by CRF (0.1 nmol/rat) and restraint stress (RS) and on castor oil-induced diarrhoea.

In colonic propulsion test, UFP_{112} mimicked the action of N/OFQ increasing the mean colonic bead expulsion time after intracerebroventricularly (icv) and intraperitoneally (ip) administration. A comparison of the effect induced on colonic transit by the same central and peripheral doses (10, 100, 250 pmol/rat) of both peptides showing significant differences ($P<0.01$) between them put in evidence that UFP_{112} is more effective than N/OFQ. These motor effects were significantly reduced by the highly selective NOP receptor antagonist, UFP_{101} (10 nmol/rat) confirming that central and peripheral NOP receptors mediate an inhibitory control on this propulsive function in rats.

The icv injections of N/OFQ and UFP_{112} inhibited CRF- and RS-stimulated fecal excretion in a dose –dependent manner; UFP_{112} was more potent than N/OFQ and its effective doses (2.5, 10, 50 pmol/rat) were 50 fold lower than those of natural peptide. In this test, UFP_{101} (0.1, 1, 10 nmol/rat) administered alone inhibited CRF- and RS-stimulated fecal excretion.

Both peptides also prevented in a dose-related fashion the diarrhoea induced by castor-oil administration. The effect of N/OFQ (500-2500 pmol/rat) and UFP_{112} (100-250 pmol/rat) on the percentage of rats with diarrhoea was significant and counteracted by UFP_{101} (10 nmol/rat) In this test, UFP_{112} was approx. 10 fold more potent than the natural peptide and produced longer lasting effects (120min).

In conclusion, all these findings indicate that, in the rat, central and peripheral NOP receptors play a role in modulating defecation and colonic propulsive motility in physiological and pathological conditions and that UFP_{112} , being more potent and effective than the natural ligand, represents a useful tool for investigating the role of the N/OFQ system in gastrointestinal functions.