THE NOCICEPTIN/ORPHANIN FQ – NOP RECEPTOR SYSTEMS AND NOVEL SELECTIVE LIGANDS

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The neuropeptide nociceptin/orphanin FQ (N/OFQ) selectively binds and activates the N/OFQ peptide (NOP) receptor. Via this mechanism N/OFQ regulates several biological functions both at central (pain, locomotion, memory, emotional responses, food intake) and peripheral (airways, cardiovascular, genitourinary and gastrointestinal systems) levels. Potent and selective NOP ligands are now required for investigating the regulatory roles played by NOP receptors in pathophysiological studies and for firmly defining the therapeutic indications of NOP receptor agonists, partial agonists and antagonists. The available and most used NOP receptor ligands are: i) the full agonists N/OFQ(1-13)NH_2, [(pF)Phe^4]N/OFQ(1-13)NH_2, [Arg^{14}Lys^{15}]N/OFQ, [Aib^{7,11}]N/OFQ, and Ro64-6198, ii) the partial agonists [F/G]N/OFQ(1-13)NH_2, Ac-RYYRIK-NH_2, and ZP-120, iii) the pure antagonists [Nphe^1]N/OFQ(1-13)NH_2, UFP-101, and J-113397. The relevant in vitro and in vivo pharmacological features of these ligands will be analysed. Moreover we recently combined in the N/OFQ sequence the chemical modifications which increase peptide potency ((pF)Phe^4, Arg^{14}Lys^{15}, Aib^7) with those which reduce (F/G) or eliminate (Nphe^1) efficacy thus generating novel highly potent and NOP selective peptide ligands encompassing full and partial agonist and pure antagonist activities. The in vitro and in vivo pharmacological profile of the full agonist UFP-112 will be presented in details. Finally, the characteristics of the recently identified non peptide antagonists SB 612111 [1] and compound 24 [2] will be analysed and compared with those of the standard NOP selective antagonists UFP-101 and J-113397.

[1] Zaratin P. F., Petrone G., Sbacchi M., Garnier M., Fossati C., Petrillo P., Ronzoni S., Giardina G. A. and Scheideler M. A. (2004) 308: 454-461.

[2] Goto Y., Arai-Otsuki S., Tachibana Y., Ichikawa D., Ozaki S., Takahashi H., Iwasawa Y., Okamoto O., Okuda S., Ohta H., and Sagara T. (2006) J Med Chem. 49: 847-849.

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