

PHARMACOLOGICAL CHARACTERIZATION OF THE NOCICEPTIN/ORPHANIN FQ RECEPTOR ANTAGONIST SB-612111: IN VITRO STUDIES

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The compound (-)-cis-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol, coded as SB-612111, was recently identified as selective antagonist for the nociceptin/orphanin FQ (N/OFQ) peptide receptor (NOP). In the present study, the in vitro pharmacological profile of SB-612111 at human recombinant NOP receptors expressed in CHO cells (receptor binding, GTP γ [³⁵S] binding, and cAMP levels experiments) as well as at native NOP receptors expressed in peripheral (mouse and rat vas deferens, guinea pig ileum) and central (mouse cerebral cortex synaptosomes releasing [³H]-5-HT) preparations was evaluated and compared to that of the standard non peptide antagonist (\pm) J-113397. SB-612111 produced a concentration-dependent displacement of [³H]N/OFQ binding to CHO_{hNOP} cell membranes showing higher affinity and NOP selectivity over classical opioid receptors than (\pm) J-113397. SB-612111 and (\pm) J-113397 competitively antagonized the effects of N/OFQ on GTP γ [³⁵S] binding in CHO_{hNOP} cell membranes (pK_B 9.70 and 8.71 respectively) and on cyclic AMP accumulation in CHO_{hNOP} (pK_B 8.63 and 7.95 respectively), being *per se* inactive at concentrations up to 1 μ M. In isolated peripheral tissues of mice, rats and guinea pigs, and in rat cerebral cortex synaptosomes preloaded with [³H]-5-HT, SB-612111 competitively antagonized the inhibitory effects of N/OFQ with pA₂ values in the range of 8.20-8.50. In parallel experiment (\pm) J-113397 was found to be 2-9 fold less potent than SB-612111. In the electrically stimulated tissues SB-612111 up to 1 μ M did not modify the effects of classical opioid receptor agonists. In conclusion, the results of the present study demonstrated that SB-612111 is among the most potent and NOP selective non peptide antagonists identified to date.

This work was financially supported by funds from the University of Ferrara (FAR grant to G.C.), the Italian Ministry of University (PRIN 2006 grant to D.R.) and by National Institute of Health (collaborative grant RO1HL71212 to D.R.).