

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.

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