PHARMACOLOGICAL CHARACTERIZATION OF THE NOCICEPTIN/ORPHANINN FQ RECEPTOR ANTAGONIST SB-612111: IN VIVO STUDIES

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The excellent pharmacological profile displayed by the selective nociceptin/orphanin FQ (N/OFQ) peptide (NOP) receptor antagonist SB-612111 ((-)-cis-1-methyl-7-[[4-(2,6-dichlorophenyl)piperidin-1-yl]methyl]-6,7,8,9-tetrahydro-5H-benzocyclohepten-5-ol) in vitro prompted us to investigate the actions of this compound in vivo. In the mouse tail withdrawal assay, SB-612111 given i.p. up to 3 mg/kg did not modify per se tail withdrawal latencies, but was able to prevent the pronociceptive and the antinociceptive action of 1 nmol N/OFQ given i.c.v. and i.t., respectively. In food intake studies performed in sated mice, SB-612111 (1 mg/kg i.p.) had no effect on food consumption, but fully prevented the orexigenic effect of 1 nmol i.c.v. N/OFQ. In 17h-food deprived mice, the opioid receptor antagonist naltrexone (1 mg/kg, s.c.) but not SB-612111 (1 and 10 mg/kg, i.p.), produced a statistically significant reduction of food intake. In the mouse forced swimming and tail suspension tests SB-612111 (1-10 mg/kg) reduced immobility time. The antidepressant-like effect elicited by SB-612111 in the forced swimming test was reversed by the i.c.v. injection of 1 nmol N/OFQ and was no longer evident in mice knockout for the NOP receptor gene. In conclusion, the present findings demonstrate that SB-612111 behaves in vivo as a potent and selective NOP antagonist, and suggest that the endogenous N/OFQ–NOP receptor system plays an important role in regulating mood related behaviors.

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