CHRONIC I.C.V. TREATMENT WITH [Nphe^{1},Arg^{14}, Lys^{15}] N/OFQ-NH_2 (UFP-101), A POTENT NOP RECEPTOR ANTAGONIST, REVERSES BEHAVIOURAL AND BIOCHEMICAL EFFECTS OF CHRONIC MILD STRESS IN RATS

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Nociceptin/orphanin FQ (N/OFQ) and its receptor (NOP) modulate several functions in the central nervous system. UFP-101 is a high affinity and selective NOP receptor antagonist that has been reported to elicit antidepressant-like effects in rodents (1). The present study investigated its effect in the chronic mild stress (CMS) paradigm. Male Wistar rats were exposed to CMS for a period of at least 6 weeks to induce a condition of anhedonia, measured as reduction of 1% sucrose solution intake, monitored at weekly intervals. Stressed and non-stressed rats (groups = 8 animals) were stereotaxically implanted with a guide cannula, at the 7th week of CMS. After appropriate recovery, the stressed groups were treated, once a day, with UFP-101 (5, 10 and 20 nmol/rat, i.c.v.), or imipramine (IMI, 15 mg/kg, i.p.), or saline for 21 days. UFP-101, reinstated sucrose solution intake within the 1st week of treatment following the highest dose (-12 % intake following 20 nmol UFP-101 vs -38% in stressed saline treated rats, $p<0.05$); at 10 and 5 nmol/rat it abolished the reduction in sucrose intake from the 2nd and 3rd week treatment, respectively (ANOVA followed by post hoc Fisher's LSD test). The restoration of sucrose consumption, once induced, remained stable up to the end of the experiment for all treatments. Rats were submitted to the forced swimming test (FST) on day 22, 24 h after the last treatment. On day 23 rats were decapitated, their blood collected to measure corticosterone (CORT) content and brains removed for 5-HIAA/5-HT analysis. In the FST, 24 h after the last administration, all UFP-101 treatments decreased the time of immobility to that of non stressed controls. IMI produced similar effects on sucrose intake and on the FST. Pre-treatment with either UFP-101 at the higher doses or with IMI completely abolished the increase in CORT induced by CMS. 5-HT turnover was increased by CSM in the frontal cortex and decreased in the pons; UFP-101, as well as IMI, were able to revert these changes to values comparable to those of non stressed controls. Repeated co-administration of N/OFQ (5 nmol/rat, from day 12 to day 21) completely prevented the behavioural and biochemical effects of UFP-101 (10nmol/rat). Our results showed that UFP-101 reversed the CMS-induced changes in behaviour, HPA axis control and central 5-HT turnover. Indeed, present findings support the view that blockade of the N/OFQ receptor signalling in the brain produces antidepressant-like effect and that the NOP receptor may represent a candidate target for innovative antidepressant drugs.

(1) Gavioli E.C. et al. (2004) Naunyn Schmiedebergs Arch. Pharmacol.369(6): 547-53.