Nociceptin receptor (NOP) knock out rats show a reduced propensity to self-administer drugs of abuse

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Substantial evidence suggests that Nociceptin/Orphanin FQ (N/OFQ) system is involved in the modulation of drug abuse and addiction-related behaviors (Ciccocioppo et al. 2000). Data from our laboratory demonstrated that intracerebroventricular treatment with N/OFQ leads to reduction of alcohol intake in rats genetically selected for excessive alcohol drinking and attenuates the rewarding effect of morphine and cocaine as measured in the conditioned place preference paradigm (Ciccocioppo et al. 2000). These data have been replicated with systemic administration of brain penetrating NOP receptor agonist such as Ro 646198 and MT-7716 (Ciccocioppo et al., 2014)
Here, to further explore the role of NOP system in addiction, we used NOP knock out (NOP-KO) rats to study cocaine, heroin and alcohol intake under operant self-administration conditions. Moreover a Conditioned Place Preference (CPP) paradigm was used to evaluate the effects of NOP deletion on the rewarding properties of cocaine. Lastly, we tested the response of NOP-KO and its wild type counterpart for saccharin self-administration.
Results showed that under fixed ration 1 (FR1) schedule of reinforcement Wistar rats rapidly acquire operant responding for cocaine (0.25 mg/0.1 ml), while NOP-KO rats showed significantly ($p<0.01$) lower lever of activity for cocaine. In a subsequent experiment in which rats were trained to take 0.25 mg/0.1 ml infusion of cocaine and then switched to a lower (0.125 mg/0.1 ml) and to a higher (0.5 mg/0.1 ml) dose of drug it was found that, compared to Wistars, at all doses, NOP-KO rats took significantly ($p<0,001$) lower amounts of cocaine.

Data from CPP induced by injection of 10mg/kg of cocaine (i.p.) showed that while, as expected, Wistar rats spent more time in the cocaine paired compartment compared to the saline paired one ($P<0.05$), no differences were observed in the NOP-KO rats.
To evaluate if this line difference was specifically related to cocaine reinforcement or could be generalized to other drugs of abuse we tested heroin (20 microg/inf) self-administration. Even in this case NOP-KO rats showed a lower pattern of heroin self-administration ($p<0.001$) compared to the wild type line.
When 10% v/v alcohol self-administration was performed we observed that NOP-KO rats self-administer significantly less alcohol compared to Wistar control rats ($p<0.05$). In addition, testing selective NOP receptor antagonist, we found that these compounds are able to attenuate alcohol self-administration in Wistar rats ($p<0.01$), but not in NOP-KO rats.
Finally, to rule out the possibility that differences between Wistars and NOP-KO might have been due to learning deficits or to a nonspecific disturbance of the reward circuitry we carried saccharin self-administration experiments. Results demonstrated that the acquisition of saccharin operant responding was equivalent between NOP-KO and Wistar rats.
In conclusion, data gathered in this study confirm that nociceptin system play a central role in modulating seeking and intake of different drugs of abuse. Importantly, this behavioural characteristic does not depend on learning deficits and does not generalize to natural rewards.
The results of this study confirm that the nociceptin system is as an important pharmaceutical target for the treatment of pathologies related to drug abuse and addiction.

Ciccocioppo et al. (2000), Peptides (7):1071-80
Ciccocioppo et al. (2000), Eur. J. Pharmacology (404):153-59
Ciccocioppo et al. (2014), Neuropsychopharmacology (11):2601-10