TARGETING THE NOCICEPTINE/ORPHANINE FQ SYSTEM TO TREAT DRUG ABUSE

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Current literature indicates that activation of nociception receptors (NOP) attenuates alcohol drinking and seeking in animal models. On the other hand, evidence supporting the hypothesis that high EtOH preference and intake are linked to upregulation of N/OFQ–NOP transmission also exists. In the attempt, to reconcile these findings we have recently undertaken a series of experiments aimed at exploring in deeper details the effect of NOP agonists and antagonists on alcohol drinking and seeking in genetically selected alcohol preferring Marchigian Sardinian (msP) rats. Results showed that alcohol intake progressively decreased with repeated NOP agonist treatment and remained low for several days after treatment discontinuation, suggesting that some agonist-induced NOP receptor reorganization must to take place to produce reductions in EtOH intake as subsequently confirmed by data revealing reduced NOP receptor expression following chronic administration of the selective NOP agonist Ro 64-6198. We, hence, conceptualized that attenuation of alcohol drinking by NOP agonists was due to receptor desensitization in response to their protracted activation, arguing that NOP antagonism should mimic the effect of chronic agonists. To confirm this hypothesis we tested the effect of the selective NOP antagonist SB 612111 on two bottle choice drinking (2BC) and yohimbine stress-induced reinstatement of alcohol seeking in msP rats. Confirming our expectation we found that NOP receptor blockade significantly and selectively attenuated alcohol intake and seeking. Saccharin consumption was not affected by SB 612111. Finally, tentative evidence suggesting that attenuation of NOP-mediated neurotransmission contributes to reduce EtOH drinking and that NOP antagonists may have “therapeutic” potential come from experiments we carried out in NOP receptor knockout rats (NOP-KO). We found in fact, that constitutive deletion of NOP receptor, resulted in a reduced motivation to drink alcohol in NOP-KO compared to Wistar wild type controls, whereas their motivation for saccharin remained intact.