THE NOCICEPTIN/ORPHANIN FQ SYSTEM AS AT TARGET FOR THE TREATMENT OF ALCOHOL ABUSE

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Alcoholism is a chronic relapsing disorder characterized by compulsive drug-seeking and use. Stress and environmental conditioning represent the major determinants of relapse in abstinent individuals. The significance of these factors for relapse risk is well documented also in the animal literature where using various reinstatement paradigms it has consistently been shown that presentation of cues predictive of alcohol availability or footshock stress elicit reinstatement of ethanol-seeking behaviour in drug-free animals. Current literature demonstrates that cue reactivity is primarily under the control of the opioidergic, dopaminergic, and glutamatergic systems. On the other hand stress-induced relapse is mainly controlled by the corticotropin-releasing factor (CRF) system. Pharmacological manipulation with the nonselective opioid antagonist naltrexone blunt cue reactivity in humans and reduces conditioned reinstatement of alcohol-seeking in laboratory animals. This compound is, however, uneffective in controlling reactivity to stress. Conversely, antagonism at CRF receptors results in prevention of stress but not cue-induced relapse.

Nociceptin/orphanin FQ (N/OFQ), the endogenous ligand of the opioid receptor-like1 (NOP) receptor, exerts marked functional antagonist effects on endogenous opioid and corticotrophin-releasing factor (CRF) systems. Moreover, evidence exists that N/OFQ modulates dopaminergic, noradrenergic and glutamatergic neurotransmission in different brain sites via presynaptic inhibitory actions. Studied conducted in our laboratories, have demonstrated that activation of NOP receptors by N/OFQ reduces ethanol self-administration, inhibits conditioned reinstatement of ethanol-seeking and prevents ethanol-induced conditioned place preference in genetically selected alcohol preferring Sardinian-Marchigian (msP) rats. Brain microinjection data also showed that the central but not the basolater amygdala or the bed nucleus of the stria terminalis mediates the inhibitory action of N/OFQ on ethanol drinking. Parallel studies conducted in Wistar rats showed that intracranial injection of the peptide also reverses several behavioural effects of stress, including stress-induced anorexia and stress-induced reinstatement of alcohol-seeking behaviour. Finally, we have used buprenorphine, a mixed opioid receptor agonist-antagonist that also activate NOP receptors to demonstrate that ethanol drinking can be controlled following peripheral injection of brain penetrating NOP agonists.

Overall these findings suggest that the N/OFQ-NOP system may have an important role in the control of alcohol related behaviours and identify this system as a promising target for “anti-relapse” medications. *Supported By: NIAAA (to RC); PRIN 2006 (To MM).*