TRANSLATIONAL RESEARCH IN POLYDRUG ADDICTION: THE ROLE OF THE NOCICEPTIN RECEPTOR SYSTEM

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Drug dependence is an etiologically and clinically heterogeneous disorder in which compulsive drug seeking and use represent core symptoms. Exposure to drugs is a necessary precondition, however, genetic predisposition together with exposure to stress and environmental conditioning factors play an important role in controlling individual vulnerability to develop dependence. The significance of the interaction of these factors has been well documented also in the animal literature where using various reinstatement paradigms it has consistently been shown that presentation of cues predictive of drug availability or footshock-stress elicit reinstatement of drug-seeking behaviour in drug-free animals. The recent development of animal models based on these paradigms has provided substantial stimulus to the development of translational research in drug addiction. Exploitation of these studies should represent a major challenge in this research area and may provide invaluable help for the identification of preventive strategies or the development of novel pharmacotherapeutic remedies. Studies conducted in our laboratory demonstrated that reinstatement of drug-seeking is triggered in rats either by drug-associated cues or stress. These effects are additive. Pharmacological dissection has demonstrated that the first component relies on activation of opioid receptors, while the latter is blocked by antagonists for Corticotropin-Releasing Factor receptors. In contrast, administration of nociceptin/orphanin FQ (N/oFQ), a recently isolated neuropeptide that is the endogenous ligand of the opioid receptor-like1 (NOP), blocks reinstatement induced by either category of stimuli. Recently, we also tested buprenorphine, a mixed opioid receptor agonist-antagonist used for maintenance therapy in opiate addicts and pain management, that also activates NOP receptors. Results showed that this compound reduces ethanol drinking in genetically selected alcohol preferring rats, an animal model of alcohol abuse, via activation of NOP receptors. Intriguingly, several clinical trials have found that buprenorphine given at high-dose (12-16 mg daily as sublingual solution, bioequivalent to 24-32 mg as tablet) significantly reduces also cocaine use by dually opiate- and cocaine-dependent outpatients. This effect is not seen at lower doses, at which buprenorphine's mu-opioid receptor agonist action would predominate. Overall these findings may suggest that buprenorphine's anti-cocaine effect at high doses, like its anti-alcohol effect, may be mediated by activation of the NOP receptor. The possibility to use buprenorphine to treat polydrug addiction will be discussed.