

THE GABAB AGONIST BACLOFEN PREVENTS RELAPSE TO DRUG ABUSE: PRECLINICAL EVIDENCE

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Detoxification from drug addiction represents the major medical problem due to high relapse rates occurring even after a prolonged drug-free period. Therefore, main goal of preclinical research in laboratory animals is to explore behavioural, environmental and neural mechanism underlying relapse and for the development of new pharmacological treatments to prevent addictive drugs relapse phenomena. Preclinical studies have reported that drugs enhancing γ -aminobutyric acid (GABA) transmission may help to reduce the consumption of several drugs of abuse and importantly, GABA_B receptors modulation has been reported to participate in drug-induced reinstatement of cocaine- and alcohol-seeking as well as in the cue-induced reinstatement of nicotine-seeking behavior in rats. These observations prompted us to conduct studies aimed at the investigation of the effect of the GABA_B agonist baclofen in drug-seeking and relapse by means of two different behavioural models of reinstatement: the intravenous self-administration (IVSA) in trained rats and the conditioned place preference (CPP) in mice.

In the IVSA reinstatement model, laboratory rats are first trained to self-administer drugs and then subjected to extinction training during which responding (i.e. lever presses) are not reinforced by contingent presentation of the drug. Reinstatement of extinguished responding (the operational measure of drug-seeking) is therefore determined after non-contingent priming injections of the drug. In a first set of experiments, we have used the IVSA model to study the effects of baclofen on heroin- and nicotine-induced reinstatement of drug-seeking behavior in abstinent rats. Results from these studies indicate that a single priming injection of either heroin or nicotine reinstates extinguished drug-seeking behavior, an effect completely prevented by intraperitoneally administration of baclofen, at a dose that does not affect responding per se.

In a second set of experiments we have used the CPP protocol to evaluate if baclofen is able to prevent the reinstatement of extinguished nicotine-induced CPP in mice. Mice were conditioned to associate a specific environment with drug injections and then subjected to extinction training during which they have been exposed to the same environment in the absence of the drug. Resumption of CPP for that environment was then determined after non-contingent priming injections of the drug. We found that nicotine induced a clear CPP after a period of conditioning and that acute nicotine primings reinstated nicotine-induced CPP following extinction, while pretreatment with baclofen dose-dependently antagonizes the effect induced by nicotine primings.

Taken together, the present results indicate for the first time that GABAB receptor activation may reduce the propensity to resume heroin or nicotine -seeking behavior thus pointing to baclofen as possible medication in maintaining drug abstinence and preventing relapse.