Chronic treatment with antidepressant drugs and memantine during abstinence following ethanol drinking in mice: Are sigma \textsubscript{1} receptors relevant for antidepressant-like effect?

G Skuza, W Sadaj, M Kabzinski

Institute of Pharmacology Polish Academy of Sciences, Department of Pharmacology, 31-343 Kraków, Poland

A significant co-morbid expression of alcoholism and depression have been shown by clinical evidences. Manifestation of the depression symptoms during abstinence increases the likelihood of relapse. The causal relationship between alcoholism and depression has not yet been established. The rewarding properties of ethanol (EtOH) as well as the development of dependence have been linked, at least in part, to the serotonergic system, thus, the use of selective serotonin reuptake inhibitors (SSRIs) in the treatment of alcoholism has been proposed. Some recent data have demonstrated development of depression-like behavior in mice during abstinence following voluntary alcohol drinking. The depression-like behavior (increase in the immobility time in the forced swim test /FST/) was observed 14 days after alcohol withdrawal. It has been recognized that sigma receptor ligands (especially sigma \textsubscript{1} agonists) reveal a potential antidepressant activity in experimental models (FST, tail suspension test) and that targeting the sigma receptors alone is sufficient (but not requisite) for production of antidepressant-like actions. As recently found, sigma \textsubscript{1} receptor knockout mice display a depressive-like phenotype. The aim of this study was to estimate the potential role of sigma \textsubscript{1} receptors in the depression-like behavior in voluntarily alcohol drinking male C57BL/6J mice. To this end, mice were allowed to self-administer EtOH (in raising concentrations of 4%, 8% and 10% v/v) in their home cages for 16 days. Then alcohol was withdrawn for 14 days (abstinence period). Desipramine, a classical tricyclic antidepressant, used as a standard drug or other drugs (fluvoxamine, sertraline and memantine) were given repeatedly (i.p., once daily) for 14 days during the abstinence period. The FST was performed on 1\textsuperscript{st} and 14\textsuperscript{th} day after EtOH withdrawal. Water control and alcohol drinking control mice received daily injections of saline. The results indicated that abstinence from voluntary alcohol drinking led to increase of the immobility time (depression-like behavior) in EtOH drinking mice vs. control non-drinking animals in the FST as well as in the tail suspension test. Desipramine, at the dose of 10 mg/kg, counteracted that effect. Fluvoxamine (10 mg/kg), and sertraline (5 mg/kg), the SSRIs with a relatively high affinity for sigma \textsubscript{1} receptors, as well as memantine (5 mg/kg), an uncompetitive glutamate/NMDA receptor antagonist, also possessing marked affinity for sigma \textsubscript{1} receptors, did not modify depression-like behavior in EtOH drinking mice (the doses of drugs under study were chosen on the basis of previous experiments). However, fluvoxamine given jointly with memantine normalized the immobility time in the FST in EtOH drinking mice. In contrast, co-treatment with sertraline and memantine, did not induce such an activity. The obtained results did not conclusively clarify the role of sigma \textsubscript{1} receptors in depression-like symptoms in mice during abstinence. Elucidation of the significance of the present findings requires further studies.

This study was supported by grant POIG. 01.01.02-12-004/09-00 from European Regional Development Fund.