

Project 9: Social Isolation Stress: Role of Neurosteroids in the Action of Ethanol on GABAAR

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Recently, it has been proposed that certain effects of ethanol could be mediated by an increase in the brain levels of neuroactive steroids, such as $3\alpha,5\alpha$ -THP, which has the ability to increase at nanomolar concentrations the GABA_A receptor function. Ethanol-induced increase in neuroactive steroid concentrations appear to result from stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, and at least in part, from a direct stimulation of brain neurosteroidogenesis. Social isolation is a model of prolonged mild stress that has been shown to be associated to marked behavioral alterations, such as increased locomotor activity, anxiety, depression, and aggressiveness in laboratory animals. Social isolation results in a decrease in the brain and plasma concentrations of neuroactive steroids, and is accompanied by an abnormal response to acute stressful stimuli as well as by an increased neurosteroidogenic effect induced by the acute administration of ethanol. We intend to use social isolation in C57BL/6J mouse strain as a model of prolonged mild stress in which to investigate further the role of neurosteroids in the acute and chronic actions that ethanol exerts on the function of GABA_A receptors in the hippocampus and amygdala and the interplay with stress. In socially isolated mice, we will measure the effects of ethanol in the following experimental condition: i) after acute administration; ii) after chronic exposure by vapor inhalation, and iii) in a free-choice drinking paradigm in order to establish if this condition can increase ethanol consumption. Neurosteroid levels in brain tissue will be assessed by RIA. GABA_A receptor gene expression by RNase protection assay, and by immunohistochemistry. GABA_A receptor function will be examined by conventional whole-cell patch clamp recording in brain slices. This project, if successful, by employing the social isolation stress will help to understand further the role of neurosteroids as endogenous mediators of certain pharmacological actions of ethanol as well as the molecular mechanisms underlying the neuronal plastic adaptive changes induced by stress and the interplay with ethanol consumption. Given that many stressful, as well as physiopathological, conditions such as PMS, depression and anxiety could be associated to marked fluctuations in plasma and brain concentrations of neurosteroids, the outcome of this study will provide additional insights about the vulnerability to ethanol abuse, characteristic of such conditions.