

## **Project 9: Social Isolation Stress: Role of Neurosteroids in the Action of Ethanol on GABA<sub>A</sub>R**

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### **A. SPECIFIC AIMS**

Social isolation has been extensively shown to be associated to marked behavioral alterations, such as increase in locomotor activity, anxiety, depression, and aggression in laboratory animals, included mice and rats, suggesting that social isolation is a stressful condition for these normally gregarious animals and that the abnormal behavioral response of rodents so reared is the product of prolonged stress.

We propose to use social isolation in C57BL/6J mice as a model of prolonged mild stress by which to investigate the role of neurosteroids in the actions of ethanol on the function of GABA<sub>A</sub> receptors in hippocampus and central amygdala. The main objective of our proposal is to evaluate the role of neurosteroids as possible mediators of the actions exerted by ethanol on the GABAergic inhibitory neurotransmission and the interplay with stress.

To accomplish our goals, the following specific aims are proposed:

- 1) Evaluate the effect of social isolation stress on hippocampal neurosteroid levels and ethanol-stimulated local steroidogenesis and on GABA<sub>A</sub> receptor gene expression and function in the hippocampus and central amygdala of C57BL/6J mice (Specific Aim 1).
- 2) Evaluate the effect of social isolation stress on the capability of ethanol to acutely increase hippocampal neuroactive steroid levels and GABA<sub>A</sub> receptor function in the hippocampus and central amygdala of C57BL/6J mice (Specific Aim 2).
- 3) Evaluate the effect of social isolation stress on hippocampal neuroactive steroid levels and GABA<sub>A</sub> receptor gene expression and function in the hippocampus and central amygdala of C57BL/6J mice given ethanol free-choice drinking during the social isolation period (Specific aim 3).
- 4) Evaluate the effect of social isolation stress on hippocampal neuroactive steroid levels and GABA<sub>A</sub> receptor gene expression and function in the hippocampus and central amygdala of C57BL/6J mice chronically exposed to ethanol vapors in ethanol inhalation chambers (Specific aim 4).
- 5) Determine whether isolation stress with/without ethanol free-choice drinking alters expression of candidate genes identified in a model of social stress induced changes in drinking (M. Miles, Project 7) (Specific Aim 5).

NOT AA-06-101 under the foreign Organizations heading. Specifically, "Proposed research should provide a unique research opportunity not available in the U.S."

The unique contribution of this work to existing projects within the INIA Consortium is its focus on stress-EtOH-neuroactive steroids interactions in the context of plastic molecular and functional changes of the GABAergic inhibitory neurotransmission. As such, this project not only fills a void in the literature related to EtOH and stress, but importantly, it targets the major overarching theme of the INIA Consortium. Furthermore, the proposed work enhances the Consortium by expanding its focus to include the animal model of social isolation stress in which ethanol abuse has been demonstrated to occur in order to provide new information about the interaction between

social stress and EtOH drinking behavior that is relevant to the INIA Consortium, as well as the alcohol field in general.

