Adolescent Social Isolation: A Rodent Model of Vulnerability to Alcohol Use Disorder and Comorbid Anxiety/Stressor Disorders

A.M. Almonte, S.E. Ewin, M.I. Mauterer, J.W. Morgan, E.S. Carter, J.L. Weiner

Although alcohol use disorder and anxiety/stressor-related disorders frequently co-occur, the neural substrates responsible for this comorbidity are not well understood. To address this gap in our knowledge, we have extensively characterized a rodent adolescent social isolation model and shown that it elicits robust, long-lasting alterations in many behaviors associated with increased risk for AUD and affective disorders, like generalized anxiety disorder and post-traumatic stress disorder. For example, relative to rats group housed throughout adolescence, adolescent socially isolated (aSI) rats exhibit increases in anxiety-like behaviors, deficits in extinction of fear learning, and enduring increases in alcohol self-administration (Butler et al., 2016). We are now using this model to identify neural substrates and circuits that contribute to the "anxiety/addiction vulnerable" phenotype engendered by this model. Our prior studies demonstrated that aSI results in profound alterations in mesolimbic catecholamine signaling as well as a significant increase in the intrinsic excitability of pyramidal neurons in the basolateral amygdala (BLA) (Karkhanis et al., 2015; Karkhanis et al., 2014; Karkhanis et al., 2016; Rau et al., 2015; Yorgason et al., 2013). These studies also provided evidence that these adaptations may play a causal role in elements of the behavioral phenotype associated with this model. Here, we will present more recent evidence characterizing the effects of aSI on synaptic transmission and plasticity in the ventral hippocampus (vHC). The vHC receives strong excitatory input from the BLA and recent studies have highlighted an integral role of this brain region in the expression of anxiety-like behaviors (Felix-Ortiz et al., 2016; Huff et al., 2016; Janak and Tye, 2015). Our initial findings suggest that aSI leads to a significant increase in vHC synaptic transmission and a reduction in theta-burst long-term potentiation (Almonte et al., 2017). Moreover, using chemogenetic approaches, we found that the selective inhibition of BLA-vHC excitatory synapses reduces anxiety-like behaviors and measures of alcohol drinking. Collectively, these studies suggest that early life stress increases excitability in the BLA and vHC and provide the first evidence for a role of the BLA-vHC circuit in the regulation of alcohol drinking behaviors.

References: Almonte, A.G., Ewin, S.E., Mauterer, M.I., Morgan, J.W., Carter, E.S., and Weiner, J.L. *Scientific Repts,* in press; Butler, T.R., Karkhanis, A.N., Jones, S.R., and Weiner, J.L. *Alcohol Clin Exp Research* 40, 1202-1214 (2016); Felix-Ortiz, A.C., Burgos-Robles, A., Bhagat, N.D., Leppla, C.A., and Tye, K.M. *Neurosci* 321, 197-209 (2016); Huff, M.L., Emmons, E.B., Narayanan, N.S., and LaLumiere, R.T. *Learn Mem* 23, 51-60 (2016); Janak, P.H., and Tye, K.M. *Nature* 517, 284-292 (2015); Karkhanis, A.N., Alexander, N.J., McCool, B.A., Weiner, J.L., and Jones, S.R. *Synapse* 69, 385-395 (2015); Karkhanis, A.N., Locke, J.L., McCool, B.A., Weiner, J.L., and Jones, S.R. *Alcohol Clin Exp Res* 38, 2770-2779 (2014). Karkhanis, A.N., Rose, J.H., Weiner, J.L., and Jones, S.R. *Neuropsychopharm* 41, 2263-2274 (2016); Rau, A.R., Chappell, A.M., Butler, T.R., Ariwodola, O.J., and Weiner, J.L. *J Neuroscience* 35, 9730-9740 (2015); Yorgason, J.T., Calipari, E.S., Ferris, M.J., Karkhanis, A.N., Fordahl, S.C., Weiner, J.L., and Jones, S.R. *Neuropharm* 101, 471-479 (2016).

Funding was provided by NIH grants AA21099, AA17531, AA26551, AA756.