Kash Elucidates the Neurocircuity of the Brain’s Stress and Anti-Stress Systems During Alcohol Drinking and Dependence

Stress is one of the most frequently cited reasons for excessive drinking in survey research and in experimental studies designed to elucidate the motivation for drinking alcohol. Stress caused by work, relationships, finances, and acute stressors such as traumatic events are common self-reported reasons for excessive alcohol consumption. Consistent with these self-reports, some studies show that alcohol consumption can increase with stress in both humans and animals and that often the more severe and chronic the stressor, the greater the alcohol consumption. Other research implicates stress as a motivation for continued drinking. Alcoholism is a chronic relapsing disorder that progressively alters stress responses to increase anxiety and negative feelings that promote drinking or relapse to drinking in individuals with alcohol dependence. Stress, accordingly, figures prominently in addiction scientists’ models of alcohol abuse and alcoholism and in psychological and behavioral approaches to treatment of alcoholism. The widely acknowledged role of stress in alcohol abuse and alcoholism notwithstanding, most of the specific mechanisms and determinants of stress-associated excessive drinking remain unknown, and the study of the biological contribution of stress to alcohol consumption and dependence is in its infancy. Furthermore, whether or not stress evokes drinking in a given individual appears to depend on numerous factors: genetics, expectations, sense of control over the stressor, past behavior, habitual coping responses, the availability of social support, and the accessibility of alcohol to name a few. Also, the specific cellular and molecular means by which stress influences alcohol consumption and dependence remain largely unidentified. Dr. Thomas Kash, Assistant Professor in UNC’s Department of Pharmacology and the Bowles Center for Alcohol Studies, is working to fill some of these knowledge gaps. His research is directed at elucidating the cellular and molecular workings of brain structures and modulators that mediate behavioral responses to stress. Kash refers to the brain structures that promote drinking and anxiety as “stress systems” and those that protect against drinking and anxiety as the “anti-stress systems.” The goal of his research group is to understand how these systems shape alcohol and addiction related behaviors on a cellular level, with an eye towards developing new methods of treating these age-old problems.

A relative newcomer to North Carolina, Kash was recruited to the Bowles Center and UNC, arriving in April 2009 from Tennessee’s Vanderbilt University, where he completed his postdoctoral research. Since joining the faculty, he has received several research grants from sources including the National Institutes of Alcohol Abuse and Alcoholism, the Department of Defense, ABMRF/The Foundation for Alcohol Research, and the Integrative Neuroscience Initiative on Alcoholism (DNIA). Each grant is devoted to elucidating specific aspects of the brain processes regulating stress and anti-stress systems related to alcoholism, drug addiction, and other psychiatric conditions.

Some of Kash’s research focuses on a brain area known as the bed nucleus of the stria terminals (BNST). The BNST is a key component of the brain’s circuitry for mediating stress responses, fear, and anxiety. This region is thought to act as a critical “way-station” in the brain, receiving information about both the external environment and internal “mental state” of the animal and then activating distinct responses, such as anxiety, arousal, and stress hormone secretion (Figure). One of the most interesting aspects of this brain circuitry is that the BNST both receives projections from and sends projections to brain regions important for regulation of emotional behavior. This interaction is normally controlled with feedback inhibition, but it has been suggested in certain pathological states, such as anxiety or depression, these interactions may lose their inhibition and become over-active. Human brain imaging studies support this possibility, as activity in the BNST is correlated with anxiety during a behavioral challenge.

In one series of experiments, Kash is characterizing changes of the neurotransmitter serotonin in the BNST and the association of changes in BNST serotonin functioning.
with behavioral manifestations of alcohol withdrawal. Serotonin is known to be involved in psychiatric conditions such as anxiety and depression, and some evidence suggests that serotonin signaling is involved in the high anxiety that can occur during alcohol withdrawal. In preliminary studies, Kash has shown that alcohol exposure alters both serotonin levels and expression of a specific serotonin receptor in the BNST, which results in anxiety. Kash is testing the hypothesis that serotoninergic signaling in the BNST is altered after alcohol exposure with resultant changes in brain function and anxiety-like behavior.

In another series of experiments, Kash is assessing the role of the neurotransmitter dopamine and its receptors in the BNST in acute responses to alcohol. In animals, dopamine appears to be elevated in the BNST after administration of alcohol, and disruption of dopamine signaling in the BNST impairs alcohol-seeking behavior. Based on preliminary data, Kash hypothesizes that the source of the dopamine that underlies alcohol responses in the BNST is a preliminary data, Kash hypothesizes that the source of the dopamine that underlies alcohol responses in the BNST is a little-studied group of dopamine neurons in a brain region known as the ventral lateral periaqueductal gray (PAG). The PAG has been implicated in a number of stress-regulated behaviors including anxiety, panic responses, and ethanol withdrawal. The cells in the PAG project to the BNST and release dopamine when they are activated. Kash is testing the possibility that chronic alcohol exposure activates dopaminergic neurons in the PAG with resultant dopamine release in the BNST, and that this activity contributes to aberrant behavior associated with alcohol dependence and withdrawal. If his hypotheses are confirmed, this understudied population of dopamine-releasing neurons in the PAG could represent a novel target for treatment of alcoholism.

Kash also studies the brain’s anti-stress systems. “It is relatively easy to make things go bad and to make brain systems malfunction,” says Kash. “We are interested in studying what we can do to make things ‘better’ for the brain and the individual. We want to identify brain systems and brain modulators that lend protection and resilience against stress. These brain systems and modulators could prove to be the most effective strategy for coping with stress and protecting against the negative impact of stressors.” Kash is currently using behavioral and cellular techniques to assess the role of neurotrophins, Y, a protein known to be part of the brain’s anti-stress systems, in neural signaling in brain areas involved in stress. As part of this research, he seeks to determine whether stress-associated changes in neurotrophin Y regulation are associated with changes in drinking in animal models. Kash is also attempting to shed light on the genetic characteristics that could underlie resilience to stress.


Website

http://www.med.unc.edu/alcohol/kash

Figure. Diagram outlining the connectivity of the BNST. The BNST receives projections from the basolateral amygdala (BLA), prefrontal cortex (PFC), and dorsal raphe (DR) and projects to the lateral hypothalamus (LH), periaqueductal gray (PAG), and ventral lateral periaqueductal gray (VLPG). There is also a serotonergic projection from the raphe to the BNST, as discussed in this article.