Spotlight on Young Investigators: Patrizia Porcu

Neurosteroids are endogenous neuromodulators that are produced in the brain, adrenal glands and gonads. These steroids have potent effects on neurotransmission mediated by gamma-aminobutyric acid type A (GABA-A) receptors inducing anti-anxiety, anticonvulsant, sedative and cognitive effects. The most potent and effective steroids of this type are known as progesterone or pregnenolone, to humans, where she has demonstrated that administration reproducibility. This assay has allowed her to extend her studies spectrometry technique and validated the assay for accuracy and recently developed a highly specific gas chromatography/mass alcohol sensitivity and alcohol’s effects on levels of THP and THDOC.

Bowles CAS Investigator Patrizia Porcu, Ph.D., Assistant Professor of Psychiatry, studies the role of neurosteroids in alcohol sensitivity and alcohol's effects on levels of THP and THDOC in various species. To facilitate her studies, she recently developed a highly specific gas chromatography/mass spectrometry technique and validated the assay for accuracy and reproducibility. This assay has allowed her to extend her studies to humans, where she has demonstrated that administration of precursor steroids, including pregnenolone or progesterone, increases levels of GABAergic neurosteroids in serum. Acute ethanol administration increases serum and brain levels of THP and THDOC in Sprague Dawley rats and this effect contributes to alcohol's actions and increases sensitivity to alcohol. Porcu has found that plasma and brain levels of the neurosteroid deoxycorticosterone are also correlated with ethanol sensitivity across 42 different mouse strains. She is exploring the genetic basis of this difference in deoxycorticosterone levels because low ethanol sensitivity is predictive of alcoholism risk in humans and heavy drinking in rodents. Indeed, she received pilot funding from a NIAAA-funded consortium to explore this idea and will present her genetic analysis this summer at the Research Society on Alcoholism meeting. Porcu has also studied species differences in the ability of alcohol to increase neurosteroids circulating in the blood. The results showed clear species differences in response to alcohol, among rats, mice and cynomolgous monkeys, with rats being the only species showing increased levels of THP and THDOC at comparable ethanol doses. Studies are underway to determine if these differences are related to the propensity to drink alcohol voluntarily.

Because neurosteroids contribute to ethanol sensitivity in both rats and humans, Porcu and colleagues in the Bowles CAS have proposed that they play a role in preventing excessive alcohol consumption in healthy subjects. Reducing excessive alcohol abuse reduces risk of alcoholism. Thus, neurosteroids may have therapeutic utility to increase ethanol sensitivity in those people with innate alcohol tolerance or restoring ethanol sensitivity in alcohol-dependent individuals. This remains an unanswered question, and Porcu's work will help lead us to the answer.

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It’s in the Molecules: Hodge Laboratory Elucidates Subcellular Mechanisms of Alcohol Dependence

A fundamental aspect of human (and animal) nature is that we repeat those behaviors that accomplish a goal, or bring pleasure. The process by which certain actions become repetitive is called positive reinforcement. Simply defined, positive reinforcement is the ability of positive, or pleasurable, events to reinforce. Using animal models, he seeks to understand the functional involvement of molecular signaling pathways in alcohol drinking and relapse. Hodge's work is based on the premise that, in alcoholism, as in other diseases, behavioral pathologies such as excessive drinking are mediated by molecular pathologies in brain systems that control natural behavioral processes, such as positive reinforcement. Hodge is particularly interested in the molecular pathologies that support behavioral pathology in the early stages of alcoholism— for example, increasing intake of alcohol over time.

Hodge and his laboratory have focused on the mitogen-activated protein kinase (MAPK) system. Found in the cells of all plants and animals, the MAPK system is a group of molecular signaling pathways that mediate numerous cellular activities and functions such as growth, differentiation, and inflammation. MAPK signaling pathways can also regulate the activity of genes and thereby can affect long-term, or enduring, functions such as learning, memory, and addiction. Of several MAPK signaling pathways that have been discovered, one—the extracellular signal-regulated kinase
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Publications


