

Center Line

Bowles Center for Alcohol Studies
School of Medicine, University of North Carolina at Chapel Hill

Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

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New Evidence for Metabotropic Glutamate Receptors As Targets for Alcoholism Therapy

All drugs of abuse produce distinct interoceptive/subjective effects that are perceived by the individual and can be distinguished from a non-drug state. For example, after drinking a glass of wine you may feel lightheaded, dizzy, sleepy or relaxed. These subjective effects represent a major controlling process that regulates drug-seeking behavior. Understanding the processes in the brain that affect these subjective effects is key to understanding how alcohol and other substances of abuse gain control over behavior in addiction.

The neurobiological mechanisms that regulate how the brain perceives alcohol are not yet fully understood. For decades, researchers have examined the glutamatergic system in the brain to better understand the effects of alcohol. Recently, a specific subtype of metabotropic glutamate receptors (mGlu5) has been identified as a potential target for new therapies for alcoholism and other drugs of abuse.

Joyce Besheer, Ph.D., assistant professor at the UNC Bowles

Center for Alcohol Studies and the Department of Psychiatry, and colleagues have recently discovered that mGlu5 receptors in the nucleus accumbens (a brain region known to modulate drug reward) regulates the subjective effects of alcohol. Using a well characterized drug discrimination procedure, rats were trained to discriminate the subjective effects of a moderate dose of alcohol from water.

Besheer examined how the subjective effects of alcohol were changed by compounds that are known to block or enhance mGlu5 receptor function. These studies, recently published in the *Journal of Neuroscience*, show for the first time that blocking mGlu5 receptors within the nucleus accumbens blunts the subjective effects of alcohol and activation of these receptors enhances the subjective effects of alcohol. "We are excited about these findings, because they show that mGlu5 receptor activity in the nucleus accumbens is critical for the perception of alcohol," said Besheer.

While it is still unclear exactly how the interoceptive effects affect drug-seeking or addiction, the results of this research suggest that mGlu5 receptors could play a significant role. "The nucleus accumbens is a central component of the brain's reward circuitry, so our results suggest the potential for overlap between drug reward processes and the interoceptive effects of drugs, especially in relation to the role of mGlu5 receptors," said Besheer. "We believe this work also highlights the importance of understanding the mechanisms that underlie the interoceptive effects of drugs." ■



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A. Leslie Morrow, Ph.D., Editor-in-Chief; Elizabeth Thomas, Managing Editor; Jane Saiers, Ph.D., Science Writer

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Malanga Lab Reveals the Basis of the "Buzz"

Many people drink alcohol for the "buzz"—those feelings of relaxation, geniality, and heightened interest that can accompany drinking in moderation. In short, mild intoxication is pleasurable and rewarding. How important is that "buzz" in the development of alcoholism? Is the "buzz" more pleasurable to some people than to others? Do inter-individual differences in the experience of alcohol-associated pleasure and reward explain why some people become alcoholics and others do not? Scientists who seek to shed light on the answers to these questions by using animal models are faced with formidable challenges. Pleasure and reward, critical motivators of alcohol drinking, are difficult to measure in studies in animals. Unlike humans, animals do not smile when they experience pleasure, and they cannot verbalize pleasurable sensations.

Dr. C. J. Malanga, Assistant Professor in the Department of Neurology and the Bowles Center for Alcohol Studies, tackles the challenges in studying reward and pleasure in animals by using the method of *intracranial self-stimulation*, a way to study the effects of drugs on the neural circuitry that underlies brain reward. In intracranial self-stimulation, animals work in order to be reinforced by delivery of electrical current directly into brain areas that mediate motivation and reward, particularly the brain's mesolimbic system. For example, an animal will spin a wheel in order to

receive electrical stimulation of the ventral tegmental area, a component of the mesolimbic system and part of the brain's reward circuitry. It is thought that intracranial self-stimulation activates the brain's reward circuitry to produce feelings of pleasure and euphoria in the same way as drugs of abuse. Animals work in order to have drugs of abuse



Malanga Lab (left to right): Elliott Robinson, BS, Megan MacFarland McGuigan, BA, Eric Fish, PhD, Elaina Howard, PhD, C.J. Malanga, MD, PhD, Thorfinn Riday, BA.

(e.g., cocaine) administered directly into certain mesolimbic brain sites in much the same way that they work to administer intracranial self-stimulation.

While drugs of abuse may differ in many respects, all of them—from alcohol to cocaine to methamphetamine—potentiate the activity of the mesolimbic system. Furthermore, all drugs of abuse that have been tested to date in the intracranial self-stimulation paradigm lower the threshold for brain stimulation reward. That is, drugs, such as cocaine, that potentiate the activity of the mesolimbic system and are pleasurable to humans reduce the amount of electrical current that is

necessary for animals to maintain responding to obtain intracranial stimulation. Reductions in brain stimulation reward thresholds reflect pleasurable activation of the mesolimbic reward system, and the lowering of the threshold for brain stimulation reward is a means of quantifying the rewarding and pleasurable effects of drugs in animals. In this model, the total amount of positive reinforcement (reward) is thought to arise from the sum of the effects of the drug of abuse and those of electrical brain stimulation on activity of the mesolimbic reward circuit. With the drug of abuse in the animal's system, the amount of electrical current needed to produce a given amount of pleasure or reward is less than when the drug of abuse is not

in the animal's system. For many years it has been known that increased release of dopamine, a neurotransmitter in the mesolimbic reward circuit, plays a key role in the reward, attention and learning associated with drug dependence. Increased electrical current increases brain dopamine and other reward transmitters providing an index of reward and reward seeking.

Intracranial self-stimulation has primarily been used in rats and larger mammals. Dr. Malanga's laboratory is one of only a handful that use the technique in mice. The availability of many genetic models in mice allows his

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Education and Training

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Publications

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Website

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lab to study the genetic basis of differences in responding in the intracranial self-stimulation paradigm. Dr. Malanga has used intracranial self-stimulation to explore in mice how prenatal exposure to drugs of abuse, particularly cocaine, impacts the rewarding effects of the drugs later in life. His lab has recently extended their studies to alcohol and to the acute rewarding effects of alcohol in adult mice.

In a recent series of studies presented in June 2009 at the Research Society on Alcoholism in San Diego, Dr. Malanga, postdoctoral researcher Dr. Eric Fish and their colleagues investigated how differences in genetic background influenced the rewarding effects of alcohol and compared the effects of alcohol with those of cocaine in the intracranial self-stimulation paradigm. This research is the first to use intracranial self-stimulation to investigate the reward-potentiating effects of alcohol; previous studies with alcohol were done in rats. Two strains of mice with different genetic make-ups and responses to alcohol were assessed: C57B16/J (C57) mice and DBA2/J (DBA) mice. The C57 mouse drinks relatively large quantities of alcohol but is not as sensitive as the DBA mouse is to alcohol's rewarding effects. The DBA mouse does not drink significant amounts of alcohol (largely because it does not like the taste and/or smell of alcohol) but appears to be more sensitive than the C57 mouse to its rewarding effects. The DBA mouse is also more sensitive than

the C57 mouse to the rewarding effects of cocaine.

Dr. Malanga and his co-investigators trained C57 and DBA mice to spin a wheel to obtain rewarding electrical current into an area of the mesolimbic reward circuit. The threshold for brain stimulation-reward was determined before and after an intoxicating dose of alcohol was orally administered. The results show that at baseline before alcohol was administered, the thresholds for brain stimulation-reward were similar between C57 mice and DBA mice. Alcohol significantly lowered the threshold for brain stimulation-reward in both strains, a finding that demonstrates that acute alcohol intoxication can be rewarding in mice (Figure). At a dose of 0.6 g/kg, alcohol lowered threshold by approximately 20% in both mouse strains approximately 15 minutes after alcohol administration. The timing of this effect mirrored the rising of alcohol concentrations in the bloodstream of these mice and is consistent with the timing of euphoria reported after ingestion of alcohol in humans.

While alcohol reduced the threshold for brain stimulation-reward in both mouse strains, the strains differed in their sensitivity to alcohol effects. Alcohol doses exceeding 0.6 mg/kg reduced brain stimulation-reward thresholds even further in DBA mice, suggesting continued reward with increasing blood alcohol levels. Surprisingly, they were ineffective in C57 mice. This pattern of

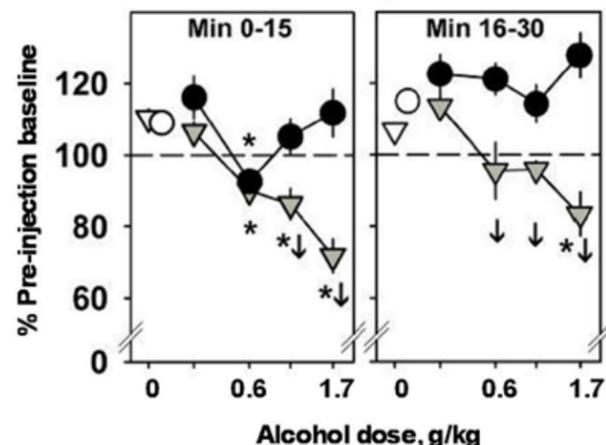


Figure: Brain stimulation reward thresholds at selected time points after administration of alcohol in C57 mice (circles) and DBA mice (triangles). Brain stimulation reward thresholds are expressed as mean percent change from the pre-injection baseline. Each panel represents the effects on brain stimulation reward thresholds during a 15-minute interval following the injection. Asterisks denote significance ($p < 0.05$) versus no alcohol (0 g/kg). Arrows denote significance ($p < 0.05$) versus C57 mice.



The Director's Column

Fulton T. Crews, Ph.D.
Director,
Bowles Center for
Alcohol Studies

One question that has always interested me is whether alcoholics experience a greater reward from drinking alcohol than other individuals. Many recovered alcoholics have told me that they remember their first drink, which I do not. I have wondered if this memory resulted from therapy to recall all the bad things alcohol caused, one of the 12 steps of AA, or if the alcohol reward was so strong, it was unforgettable. Is it the buzz that drives drinking individuals to progress from experimentation to abuse to addiction?

Dr. C.J. Malanga has discovered that genetically different strains of mice show unique reward responses to alcohol, strongly suggesting genetic components of reward. This is almost impossible to do in humans because we have learned so much about alcohol that our response is blurred by what we learned. For example, those who have learned that alcohol or cocaine are dangerous will have more negative responses than those who have learned that these drugs make you feel good. Learned responses differ from innate biological responses and studies in adult humans cannot distinguish between them. Malanga has shown genetic differences in the innate reward response in the brain. Reward thresholds provide insight into how reward impacts the addiction process.

Dr. Joyce Besheer uses animals to identify the brain circuits that determine how alcohol "feels." What makes alcohol consumption a unique experience? What alcohol responses are learned with drinking experience? Understanding those learned responses will help understand the drive that takes control over

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results suggests that the degree to which alcohol is perceived as rewarding in the intracranial self-stimulation paradigm differs between the mouse strains.

Dr. Malanga and his colleagues assessed the effects of cocaine, as well as alcohol, on the threshold for brain stimulation-reward in these studies. By studying cocaine, a drug of abuse with a different mechanism of action than alcohol, the investigators sought to determine whether their results with alcohol were specific to alcohol or reflected generalized differences in the responsiveness of the mesolimbic dopamine system to drugs of abuse regardless of pharmacological mechanism of action. They found that, like alcohol, cocaine lowered the brain stimulation-reward threshold in both mouse strains but was more potent in DBA mice than in C57 mice.

"We have shown with the intracranial self-stimulation paradigm that mild alcohol intoxication potentiates the mechanisms of brain reward," says Dr. Malanga. "The intracranial self-stimulation method is powerful in that it allows

alcoholics. Together these approaches point to the same brain regions that underlie the motivation to consume alcohol. We are pleased to have these promising young scientists involved in our Center's research program and intellectual environment. We expect continuing great progress from both of them.

We are also pleased to honor one of our senior professors, Dr. George Breese, with a John Andrews Distinguished Professorship. Dr. Breese is a leader in studies of the GABA-mimetic effects of ethanol, unique brain region sensitivity to alcohol and how alcohol abuse leads to anxiety and craving for alcohol. He has made discoveries in neuropharmacology for over 40 years. The distinguished professorship will support his continued research and scholarship so he can focus on his studies of the mechanisms that underlie protracted ethanol withdrawal anxiety. John Andrews wanted to support research that will lead to new treatments for alcoholism. We believe that Breese's work is likely to do just that. ■

CONGRATULATIONS

to
Dr. George Breese
on Receiving the
John R. Andrews
Distinguished Professorship

This professorship recognizes leaders in alcohol research for their outstanding work in finding cures, genes, causes and treatments for alcoholism and alcohol use disorders.

us to measure changes in brain reward repeatedly and across different drugs and multiple drug doses. We are now in a position to investigate the pharmacological mechanisms for the effects of alcohol and cocaine on the brain reward circuits. We also want to explore the consequences of prenatal or repeated or chronic alcohol adult exposure in this model, and the impact of other experiences that would be expected to alter the brain's sensitivity to reward. Our findings will help us define the neural and pharmacological substrates of alcohol drinking, which we can then explore further with neuroanatomical and *in vitro* electrophysiological methods. By knowing better how drinking is motivated, we will know better how to use tools and interventions that affect perception of reward to curb drinking when it is excessive. With the mouse models, we also have the opportunity to further explore the genetic determinants of motivation to drink. The sky is the limit. ■