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 of 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. Intracranial self-stimulation, animals work in order to be recompensed 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 necessary to 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
Figure: Brain stimulation reward in C57 and DBA/2J mice. Circles represent 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.

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 the first time they drank alcohol, it had such a profound and unique experience? What alcohol responses are learned with drinking experience? Understanding those learned responses will help understand the drive that takes control over alcoholics. Together these approaches point to the same brain regions that underlie the motivation to drink alcohol. We are pleased to have these promising young scientists involved in our Center's research program and intellectual environment. We expect continued 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 GABAAergic 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.

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lab to study the genetic basis of differences in responding to 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 its 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-up and responses to alcohol were assessed: C57Bl/6j (C57) and DBA/2j (DBA) mice. The C57 mouse is highly sensitive to the rewarding effects of alcohol, whereas the DBA mouse is less sensitive. The authors used both strains as a way to evaluate the impact of genetic differences on the rewarding effects of alcohol.

Results suggest 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 co-investigators trained C57 and DBA mice to spin a wheel to obtain rewarding electrical current into an area of the mesocorticolimbic 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.

The authors found that C57 mice 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 results suggests that the degree to which alcohol is perceived as rewarding in the intracranial self-stimulation paradigm differs between the mouse strains.


Asterisk denotes significance (p<0.05) versus alcohol (0 g/kg). Arrows denote significance (p<0.05) versus C57 mice.