UNC Researcher Receives K01 Award to Develop New Research Directions

Sandeep Kumar, M.D., assistant professor of psychiatry and member of the Bowles Center for Alcohol Studies, recently received the Mentored Research Scientist Development Award (K01) from the National Institutes of Health (NIH) to develop an independent research program that extends his post-doctoral research in new directions. Dr. Kumar is collaborating with mentor A. Leslie Morrow, Ph.D. to elucidate the molecular mechanisms that underlie alterations in γ-aminobutyric acid type A ($GABA_A$) receptor adaptations that influence the development of ethanol dependence. He is focusing on the role of receptor trafficking in mediating $GABA_A$ receptor adaptations. The award will provide Dr. Kumar with training in confocal microscopy to investigate receptor trafficking or movement between the cell membrane and intracellular compartments and the use of transgenic mouse technology. His research efforts also include collaborations with senior scientists to develop new methods for investigating the phosphorylation of $GABA_A$ receptors in brain tissue. His new studies will provide important mechanistic information on the molecular basis of ethanol-induced adaptations in $GABA_A$ receptors that influence the development of ethanol tolerance and dependence.

Sandeep Kumar, M.D.

Dr. Kumar completed undergraduate and medical studies at the Ranchi University, India. He completed a residency in Radiology at the Rajendra Medical College, India, and came to the United States to undertake research fellowships at Wake Forest University and the University of North Carolina at Chapel Hill. Dr. Kumar first worked in alcohol research as a post-doc with Dr. A. Leslie Morrow, associate director of the Bowles Center and professor of Psychiatry and Pharmacology. He trained in biochemical techniques including chloride flux assays and protein expression methods. Successful in his previous endeavors, he wants to expand his training and horizons to address new questions and begin his own research program. When speaking of his experience at UNC, Dr. Kumar said, "I have benefited immensely from the mentoring of Dr. Leslie Morrow and the intellectual environment of the Bowles Center. My exposure to alcohol research greatly influenced my decision to pursue a career in research rather than clinical practice." ■

The Bowles Center for Alcohol Studies

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

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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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Research by UNC Scientist Reveals Alcohol-Specific Neural Substrate in the Brain's "Reward Circuit"

Cocaine, alcohol, food, gambling, sex, plastic surgery: the list of substances and activities to which addictions are said to be established is long and growing. Neither lay people nor scientists dispute the existence of addictions to psychoactive substances such as cocaine or alcohol. However, whether addictions also develop to basic physiologic requirements such as food and sex and to higher-order behaviors such as gambling is controversial. Addiction involves the compulsive need for and use of a substance, and establishment of an addiction (at least in its early stages) entails behavior motivated by the goal of achieving reward or reinforcement. Are all rewards created equal, and is it accurate to label the gamut of compulsive, excessive behaviors directed at these rewards as *addictions*? Is the cocaine addict motivated by the same drives as the compulsive gambler? Is the overeater who attempts to diet but feels helpless to control his eating confronted by the same physical and psychological challenges as the alcoholic who tries to but cannot abstain from drinking?

Dr. Donita Robinson, Assistant Professor in the University of North Carolina's Psychiatry Department and the Bowles Center for Alcohol Studies, is approaching answers to some of these questions by studying the neural underpinnings of reward-seeking behavior in animals. With collaborator Dr. Regina Carelli of UNC's Psychology Department, Robinson is investigating a brain area known as the nucleus accumbens. Often characterized as a main component of the brain's "reward system," the nucleus accumbens receives converging neural input from brain areas involving memory, emotion, and information processing—functions integral to goal-directed behavior. Neuroscientists consider the nucleus accumbens an important neural substrate for motivated behavior involving "natural" rewards such as water, food, and sex. According to a major hypothesis in drug abuse research, the nucleus accumbens is also an important neural substrate for motivated behavior involving drugs of abuse. It is postulated that addictions can be so difficult to overcome because they tap into the same brain circuits that evolved to ensure that the organism seeks and obtains those rewarding substances, such as food and water, that are necessary for sustaining life.

Robinson and Carelli Alcohol Research Group: Wilbur Williams, Regina Carelli, Ph.D., Donita Robinson, Ph.D., Amber Kinard, and Scott McConnell

Robinson studies neural correlates of alcohol-motivated behavior in the nucleus accumbens of rats in a paradigm similar to that previously employed by collaborator Carelli to study neural correlates of cocaine-motivated behavior. Carelli measured the electrical activity of single nerve cells (neurons) in the nucleus accumbens in rats trained to press a lever to receive an intravenous infusion of cocaine. She found that specific subsets of neurons in the nucleus accumbens appear to encode for different aspects of goal-directed responding for cocaine. Some neurons exhibited changed (either increased or decreased) electrical activity immediately before the rat pressed the lever whereas others exhibited such changes within seconds after the lever press. No such changes were observed in rats pressing a lever that was not associated with cocaine reward.

To test the hypothesis that the same neural circuitry that mediates goal-directed behavior involving "natural" rewards also mediates goal-directed behavior involving drugs of abuse, Carelli went on to examine whether the same neurons are activated when animals engage in goal-directed behavior for cocaine and natural (water) reward. She found that specific neurons in the nucleus accumbens encoded for responding for water and food; however, only 8% of those same neurons were activated during goal-directed behavior involving

Continued on next page

Donita Robinson, PhD

Experience
Assistant Professor, UNC Department of Psychiatry and Bowles Center for Alcohol Studies

Education
Post-doctoral training in neurochemistry, University of North Carolina at Chapel Hill, 2000-2002; Ph.D. in neuroscience, University of Texas at Austin, 2000; M.A. in biopsychology, University of Michigan at Ann Arbor, 1993; B.A. with honors and special honors in psychology, University of Texas at Austin, 1991.

Recent Publications

Robinson DL, Volz TJ, Schenk JO, Wightman RM. Acute ethanol decreases dopamine transporter velocity in rat striatum: in vivo and in vitro electrochemical measurements. Alcohol Clin Exp Res. 29(5):746-55 (2005).

Robinson DL, Wightman RM. Nomifensine amplifies subsecond dopamine signals in the ventral striatum of freely-moving rats. J Neurochem. 90(4):894-903 (2004).

Robinson DL, Venton BJ, Heien ML, Wightman RM. Detecting subsecond dopamine release with fast-scan cyclic voltammetry in vivo. Clin Chem. 49(10):1763-73 (2003).

Phillips PE, **Robinson DL**, Stuber GD, Carelli RM, Wightman RM. Real-time measurements of phasic changes in extracellular dopamine concentration in freely moving rats by fast-scan cyclic voltammetry. Methods Mol Med. 79:443-64 (2003).

Website
http://www.psychiatry.unc.edu/directories/Robinson.htm

Research supported by NIAAA.

cocaine. The overlap was much greater during responding for two "natural" rewards: approximately 70% of neurons studied had similar responses to the "natural" rewards of water and food. These results suggest that, while the nucleus accumbens is a neural substrate for behavior involving both "natural" rewards and cocaine, different microcircuits in the nucleus accumbens encode for natural-reward-mediated behavior versus cocaine-mediated behavior.

Robinson has modified and extended this paradigm to study the effects of goal-directed behavior for alcohol on neural activity in the nucleus accumbens. Like cocaine, alcohol is a psychoactive substance and a drug of abuse. Unlike cocaine, alcohol is a liquid consumed by rats in a manner identical to consumption of water. Robinson sought to know whether responding for alcohol is encoded similarly to responding for water in the nucleus accumbens. In her experiments, rats trained to press one lever to obtain water and another lever to obtain alcohol were given simultaneous access to the levers. As in Carelli's research with cocaine, a subset of neurons in the nucleus accumbens appeared to encode for the reinforced response by changing their electrical activity just before or just after the lever press. Robinson identified some neurons that encoded for responding for alcohol alone; others encoded responding for water alone; and still others had a similar pattern of change in electrical activity for alcohol and water (Figure). Robinson presented these results at this year's Society for Neuroscience meeting in Washington, DC.

Robinson's and Carelli's research provides new insights into the neural basis of goal-directed behavior. Consistent with current understanding, their research shows the nucleus accumbens, an integral part of the brain's reward circuit, to be important in processing information about motivated responding involving "natural" rewards as well as drugs of abuse. Their research augments current understanding by showing that the neural substrate for reward-motivated behavior is not one-size-fits-all. The microcircuits activated during responding for alcohol, a drug of abuse, do not wholly overlap with those activated during responding for water, the natural reward. The neural response does not overlap despite identical response requirements to obtain the reward (i.e., a lever press) and despite identical modes of consumption of the rewards (i.e., drinking). Robinson's research thus shows that all rewards are *not* created equal—at least as far as neurons in the nucleus accumbens are concerned. These findings and results of her ongoing and planned research will help to shed light on the nature of compulsions and addictions (To what degree are the neural substrates for compulsive eating and compulsive drinking similar?) and lead to interventions tailored to specific compulsive and addictive behaviors. ■

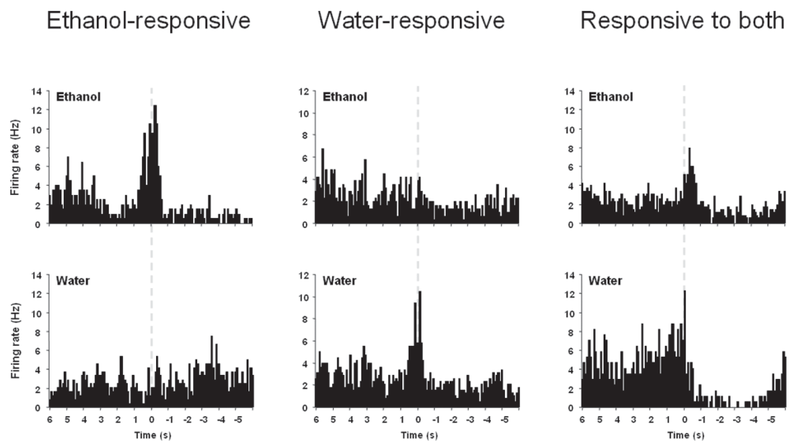

Figure 1. Examples of nucleus accumbens neurons that show phasic firing rates around the lever press for ethanol or water. The average firing rate across trials (ethanol trials on top, water trials on bottom) is plotted versus time with the lever press at time zero (dashed line). Rats had concurrent access to ethanol and water. The cell on the left is responsive to ethanol but not water reinforcement, as the firing rate increases immediately prior to the lever press for ethanol. The cell in the middle shows the opposite orientation. The cell on the right shows phasic activity to both ethanol and water responding, but with different firing patterns.

The Director's Column

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

This issue of the Centerline highlights two new junior faculty who are carrying the cutting edge of alcohol research forward. Alcohol is a complicated drug. Although alcohol shares some similarities to cocaine and other addictive drugs, it is unique in many ways. Alcohol requires high doses, contains significant calories and produces systemic inflammatory and hormonal effects that contribute to it's actions. The complex nature of alcohol , both a drug and a source of calories like food, are factors that need to be addressed in experimental design and interpretation of results. These are not trivial concerns, but complicated components of alcohol research studies, important to consider if we are going to understand the actions of alcohol that lead to addiction, organ disease and birth defects. Both Drs. Robinson and Kumar are learning the complexities of alcohol experimentation as well as the key elements of alcohol dependence that relate to their studies.

Alcoholism and human alcoholic disease are common in society. Of those needing medical treatment in hospitals and clinics, many have alcohol problems that contribute to their poor health and/or accidental injury. Young scientists often avoid alcohol studies, in part due to the complexities of experimenting with alcohol. Although much of what modern medicine knows about alcoholism is the result of biomedical research in animals and cells, getting animals to drink like humans or even administering it is difficult. Some strains of mice and rats like to drink and some have been bred to drink, but still they will not readily drink like human alcoholics. Animal models can mimic various aspects of human alcoholism including alcohol dependence, but none are complete. Animal studies have been valuable in understanding the neurobiology of motivation and reward associated with addiction as well as the anxiety and withdrawal symptoms associated with cessation of drinking. Further, animal models first discovered that anti-opiates like naltrexone reduce drinking, leading to the use of this medication to assist maintenance of abstinence during treatment for human alcohol dependence.

These discoveries and the discoveries of the future that will lead to better treatments of addiction, organ disease and other maladies require well trained and experienced scientists knowledgeable about alcohol, its complicated biology, and how models of pathology can be used to understand disease. The Bowles Center is training new junior scientists by providing them with the knowledge necessary to sort out the experimental complexities of alcohol as well as the pathology associated with excessive alcohol consumption. These new young faculty represent the future of alcohol research. Their efforts will lead us in new directions to prevent and reverse alcoholic disease. We are excited about the progress of Drs. Robinson and Kumar and look forward to nurturing their development and learning about their new discoveries. ■

Post-Doctoral Fellowships Now Available!

The Bowles Center for Alcohol Studies is offering post-doctoral fellowships in a multidisciplinary training program funded by NIAAA. Research is focused on molecular and cellular studies on alcohol actions.

Applicants must have an M.D. or Ph.D., U.S. citizenship or permanent residency, and an interest in alcohol research. Send applications to a faculty mentor of interest.

George Breese, Ph.D.
Actions of ethanol on ion channels

Fulton Crews,Ph.D.
Neurodegeneration, neurogenesis and addiction

J. C. Garbutt, M.D.
Pharmacotherapy for alcoholism

Clyde Hodge, Ph.D.
Behavorial pharmacology and pharmacogenomics

A. Leslie Morrow, Ph.D.
Molecular mechanisms of alcohol dependence

David H. Overstreet, Ph.D.
Serotonergic mechanisms of ethanol self-administration

Ivan Rusyn, M.D., Ph.D.
Mechanisms of alcohol-induced carcinogenesis

Kathleen Sulik, Ph.D.
Mechanisms of alcohol-related birth defects

Todd Thiele, Ph.D.
Molecular basis of voluntary ethanol consumption

Michael Wheeler, Ph.D.
Inflammatory response in liver injury and regeneration

Mark Wightman, Ph.D.
Electrochemistry of drug responses

Send your CV and statement of interest to faculty at:

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