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UNC Scientist Studies Rapid Dopamine Release and Alcohol Drinking

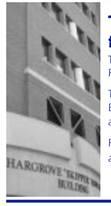

Donita Robinson, Ph.D.

Dopamine is a neurotransmitter that influences key brain systems that control movement, emotional response, cognition, and ability to experience pleasure and pain. For years, researchers have studied dopamine's role in addiction. UNC's Donita L. Robinson, Ph.D., a research associate of Chemistry and research assistant professor of Psychiatry, is using state-of-the-art technology to study the association between dopamine and alcohol addiction. While traditional measurements of changes of dopamine concentrations in the brain have operated on a timescale of minutes to hours, Dr. Robinson uses *fast-scan cyclic voltammetry* to detect changes on the subsecond timescale, in real time. The resulting extracellular signals are called *dopamine transients*, due to the fact that they reach concentrations of up to 1 μM but for just a second or two. Much of her recent work has focused on the characterization of these dopamine signals to determine their significance in natural and experimental situations, including alcohol drinking.

Dopamine transients were first shown in response to electrical stimulation of dopamine neurons in a way that mimicked burst-firing. However, Dr. Robinson's research demonstrated that similar signals occur naturally during behavior. Her first experiments measured dopamine in the nucleus accumbens, a brain region involved in reinforcement, during the natural rewards of sex and social interaction. Dopamine transients were measured in male rats when receptive females were put into the cage and during subsequent sniffing and investigation. These remarkable data were the fastest measurements of neurotransmitters recorded in vivo to date — not just of dopamine, but of any neurotransmitter. Dr. Robinson has since characterized these transients: where they occur, how often, and what triggers them. Her research shows that the dopamine signals appear to be triggered by important stimuli in the animal's environment and, in turn, facilitate appropriate response behavior. Consistent with this, her preliminary data suggests that dopamine transients occur more frequently when rats drink alcohol.

Dr. Robinson completed her doctoral education in neuroscience at the University of Texas at Austin. She recently conducted post-doctoral training in neurochemistry in the laboratory of Dr. Mark Wightman at UNC, the scientist who developed fast-scan cyclic voltammetry. "One thing that has been fruitful for me is to have a hand in different projects and to develop active collaborations." She values her training experience with members of the Bowles Center such as Dr. Wightman, who has worked closely with her on her dopamine research, and Dr. David Overstreet, who collaborated with her to study of dopamine transients in alcohol-preferring P rats. Such interaction has been crucial for her understanding of concepts, development of new ideas and career advancement.

The focus of Dr. Robinson's research switched to alcoholism from other addictive drugs and Parkinson's disease during graduate school, "As I was in the lab and learned more about alcoholism's social and economic impact on the country and families. I decided that even though it was more challenging than other drugs, it's definitely more useful to study because it affects so many more people."



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Center Line, Vol. 14 No. 2 *Published quarterly to bring greater understanding of alcoholism research and the Center's mission.*
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Bowles Center for Alcohol Studies
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Our mission is to conduct, coordinate, and promote basic and clinical research on the causes, prevention, and treatment of alcoholism and alcoholic disease.

ISSN 0738-6567 Volume 14, Number 2, 2003

Unlocking the Secrets of the Hepatic Stellate Cell:
UNC Researchers Shed Light on Mechanisms Underlying Liver Disease


The Rippe Research Team: (L to R)Terry Morris, Ramón Bataller, Jeff Lindquist, Richard Rippe, Chris Parsons, and Shigeki Tsukada

The National Institute of Alcohol Abuse and Alcoholism estimates that more than two million Americans suffer from alcohol-related liver disease, which is the third most common cause of death after heart disease and cancer in Americans ages 45 to 65 years. In western countries, mortality from alcohol-related liver disease, unlike other major killer diseases such as heart disease, has increased over the past decade. For example, in a study published in the *British Medical Journal* in 2002, researchers found that deaths from liver disease in the West Midlands of England doubled from 6 per 100,000 persons in 1993 to 12.7 per 100,000 persons in 2000 (*BMJ* 2002;325:312-313). Although liver disease can arise from several causes other than alcohol, the increase in liver disease-associated mortality in this study was attributed almost wholly to alcoholic liver disease, which caused nearly three times more deaths in 2000 than 1993. These sobering statistics highlight the need for measures to prevent and treat alcohol-related liver disease.

Dr. Richard Rippe, of the Bowles Center for Alcohol Studies and the Department of Medicine at the University of North Carolina, studies the mechanisms that cause liver disease brought on by excessive use of alcohol and other substances. By determining precisely how the liver fails when it is exposed to certain substances, his research team hopes ultimately to identify means of preventing and treating liver disease.

Early stages of alcohol-associated liver disease are manifested by *fibrosis*, in which liver tissue becomes tough and thick. Later stages are manifested by *cirrhosis*, in which healthy liver tissue is replaced with scar tissue that cannot perform the vital functions of the normal liver —metabolizing cholesterol, storing energy, metabolizing drugs and toxic substances, and regulating the levels of sugar and hormones in the bloodstream. Cirrhosis is incurable and eventually leads to death because the body cannot function without a healthy liver. Rippe's research focuses on the processes that are responsible for fibrosis. In fibrosis, liver cells called *hepatic stellate cells* switch from their normally quiescent state to an activated state where they overproduce certain proteins, such as type I collagen, to toxic levels. Type I collagen and other overproduced proteins are partly responsible for the toughening and thickening of liver tissue that occurs in liver disease. In the healthy liver, type I collagen accounts for one-twentieth of the total protein content, whereas type I collagen accounts for one-half of the total protein content of the cirrhotic liver. Some of Rippe's work is devoted to determining why, at the cellular and molecular level, type I collagen is overproduced by hepatic stellate cells.

In a series of recent experiments, Rippe's team identified molecular factors that trigger activation of the gene that produces type I collagen. Rippe approached this question by assessing the role of *deoxyribonuclease I-hypersensitive sites* that are located near the promotor of the α1(I) collagen gene. He determined which sites activate the promotor region to induce collagen gene expression and excess protein production. Different mouse strains were developed that contained different deoxyribonuclease I-hypersensitive sites positioned upstream of the promotor region of the α1(I) collagen gene that controlled expression of a green fluorescent protein. When the gene promoter was activated in these mice, cells would appear bright green under ultraviolet light. Cells not containing the activated gene, on the other hand, did not fluoresce.

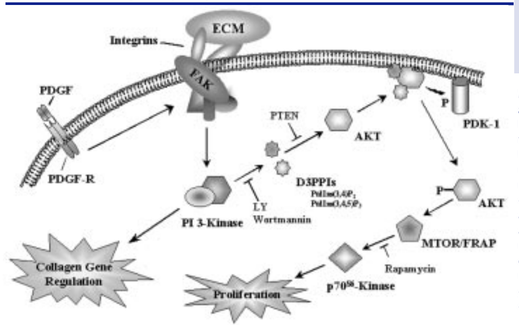
Rippe found that green fluorescence reflecting gene activation was much stronger and occurred earlier in mouse strains that had certain specific deoxyribonuclease I-hypersensitive sites (type 4,5) positioned upstream of the promoter region of the gene. In mouse strains where other deoxyribonuclease I-hypersensitive sites were tested, the fluorescence response did not occur. Similar effects were observed in hepatic stellate cells in culture and cells exposed to a fibrogenic stimulus in the living animal. Thus, he found a specific molecular target regulating activation of

the α1(I) collagen gene when it is exposed to a fibrogenic stimulus. Possibly, a similar mechanism is involved in humans whose liver cells are exposed to excessive alcohol. This target could be one key to stopping the progression of liver fibrosis.

In addition to overproducing type I collagen and other proteins, hepatic stellate cells proliferate in response to fibrogenic stimuli such as alcohol. In liver disease, the proliferation of hepatic stellate cells is thought to be harmful as it amplifies the population of cells overproducing proteins that contribute to liver scarring and malfunction. In another series of experiments, Rippe and his laboratory investigated the molecular mechanisms underlying proliferation of hepatic stellate cells. They found that three proteins—focal adhesion kinase, phosphatidylinositol 3-kinase (PI 3-kinase), and Akt—are integrally involved in transmitting signals that tell the hepatic stellate cell to proliferate (See figure). All of these proteins are part of one signaling pathway that contributes to cellular proliferation. Proliferation of hepatic stellate cells in response to a fibrogenic stimulus was reduced, but not eliminated, by blocking one or more of these proteins. The latter finding suggests that the hepatic stellate cell has multiple, redundant pathways that control proliferation. Proliferation can be reduced by blocking one pathway, but the functioning of other, redundant pathways may explain the finding that proliferation does not stop.

Rippe and his laboratory also found evidence that some of the same cellular signals that are involved in fibrogenesis are also involved in proliferation. For example, inhibition of PI 3-kinase, a protein important in proliferation of hepatic stellate cells, also reduced production of type I collagen protein by hepatic stellate cells. This finding suggests that PI 3-kinase is important in type I collagen production (See figure). Rippe and his colleagues are now investigating the effects of inhibition of PI 3-kinase in an animal model of fibrosis. They hypothesize that inhibiting PI 3-kinase will reduce or inhibit fibrosis.

"We're excited about these findings," says Rippe. "The data suggest that the focal adhesion kinase-PI 3-kinase-Akt pathway may constitute a therapeutic target to modulate the fibrogenic response in the liver. PI 3-kinase may also represent a potential therapeutic target for modulating hepatic stellate cell proliferation resulting in reduced fibrosis following a fibrogenic stimulus, like ethanol. We think that effective treatments for liver disease should be directed at inhibiting one or both of these processes occurring in activated hepatic stellate cells—fibrogenesis and proliferation," says Rippe. "By blocking fibrogenesis and/or proliferation early, we could help to derail the degeneration from fibrosis to cirrhosis to death that occurs in so many alcoholics."



Phosphatidylinositol-3 kinase (PI3-K) signaling in the hepatic stellate cell. PI3-K signaling has been shown to transmit proliferative signals in the hepatic stellate cell. Our laboratory has recently demonstrated that PI3-K signaling controls type I collagen gene expression in the hepatic stellate cell as well. We believe that this is mediated in part by transcriptional mechanisms as well as by stabilization of the α1(I) collagen mRNA molecule. These recent findings make PI3-K a prime target for therapeutic intervention in alcohol-induced liver fibrosis.

Richard Rippe, Ph.D.

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Education:
Ph.D., 1988, University of Arizona
M.S., 1983, Northern Arizona University
B.S., 1976, Indiana University

Recent Publications:

Taimr P, Higuchi H, Kocova E, Rippe R, Friedman S, Gores GJ (2003). Activated Human Stellate cells express the TRAIL receptor-2/death receptor-5 and undergo TRAIL-mediated apoptosis. Hepatology 37:87-95.

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Webpage: http://www.med.unc.edu/alcohol/faculty/Rippe/Rippe.htm

Research partially funded by NIAAA.

The Director's Column

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

This issue of the Centerline illustrates the way scientific research on the effects of alcohol on the liver and brain relate to common health care issues. Dr. Richard Rippe's research efforts seek to identify the molecular mechanisms controlling the promoter region of the collagen gene that relates to alcoholic liver fibrosis and the progression to cirrhosis. Dr. Donita Robinson's studies of limbic brain structures involve electrochemical and electrophysiological indices related to addiction and recovery. The diversity of these stories illustrates the challenges of translating the knowledge of modern molecular medicine to improved health. It is imperative that researchers and health care professionals work together to learn and develop strategies to improve health care.

As an NIAAA-funded Alcohol Research Center we are fortunate to have funding to hold an education conference with the goal of educating primary care health professionals, particularly family and general physicians. One part of this goal is to relate our Center's research to clinical practice to help improve health care. Our conference, "Understanding and Treating the Spectrum of Alcohol and Substance Abuse Problems," will address the health risks and benefits associated with alcohol use - since patients commonly ask health care providers for this information. Evidence that current therapies for addiction are effective will be presented. The power of primary care interventions and instructions on how to conduct them could have a significant impact and might improve health care in North Carolina as a direct result of the conference. The importance of families and adolescent environment as well as multiple diagnoses will be covered. Pathologies associated with alcohol abuse will be covered by one of our physician scientists, Dr. Michael Fried, who will also mention the importance of collagen in fibrosis and cirrhosis. Although it is truly a challenge to relate focused and highly esoteric cutting-edge science to primary health care, I like this challenge.

Cancer researchers and clinicians have translated molecular studies to improved health care. Biopsy, blood antigens and other molecular measures are used to diagnose, quantitate disease and direct therapy. Molecular measures assist in carcinogenic risk of exposure to environments; however, behavior contributes to risk of cancer. Smoking may be the most difficult high-risk behavior related to cancer and is an addictive behavior that is hard to modify. Modern molecular studies provided the proof of the relationship between smoking and cancer that prompted large nonprofit organizations and the public to try to change smoking behavior. Approximately 30 years ago, President Richard Nixon declared war on cancer and modern molecular science is translating that effort. The National Cancer Institute is the largest of all the National Institutes of Health as a result of the war on cancer. Cancer researchers and clinicians can currently bridge the continuum between modern molecular medicine, the genome and the use of this information to improve health.

In order to greatly improve the health of individuals suffering from alcoholic disease and prevent more cases, we need the molecular understanding to establish the risks, to quantitate the pathologies of addiction and to direct therapy. For decades, there has been a war on drugs – mostly fought by the police. When we convert the war on drugs to a modern molecular medicine effort, the rate at which discoveries translate to practice will be more rapid and will lead to the improvement of the general health of our society. This challenge will be even more fun.

Alcohol & Substance Abuse Treatment Education Conference

September 20, 2003

The Bowles Center for Alcohol Studies will hold a one-day conference at the Ida and William Friday Center for Continuing Education entitled "Understanding and Treating the Spectrum of Alcohol and Substance Abuse Problems." The program is designed for clinicians practicing in North Carolina, including primary care physicians, emergency physicians, psychiatrists, nurse practitioners, physicians' assistants, social workers and substance abuse counselors. The faculty for the conference include national and local experts.

Topics include:

- risks and benefits of alcohol consumption
- adolescence and risks for addiction
- office intervention with risky drinkers
- medical and psychiatric problems caused by alcohol
- medication used to treat alcohol dependence

The conference will take place in September which is "Recovery Month" and the organizers are planning a reception immediately after the conference to celebrate recovery from addiction.

For further information visit **www.med.unc.edu/alcohol** or contact UNC's Center for Continuing Medical Education at 919-962-8886 or deedra_donley@med.unc.edu.

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