

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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Hodge Lab Makes New Strides in Understanding the Molecular and Cellular Basis of Alcohol Reinforcement

Ask neuroscientists, neurologists, psychiatrists—anyone whose work involves brain function—about important recent developments in their field, and glutamate is likely to be mentioned. The brain's main excitatory neurotransmitter, glutamate is found throughout every brain region. Glutamate activates brain cells (neurons) by interacting with various types of neuronal receptors that are widely distributed throughout the brain. The ubiquitous nature of glutamate and the widespread distribution of glutamate receptors throughout the central nervous system are consistent with the fundamental role this neurotransmitter appears to play in brain function. Glutamate has been implicated in mediating diverse functions including attention, movement, learning, and memory. Likewise, abnormal glutamate neurotransmission has been implicated as a primary cause or contributor to several neurologic and psychiatric diseases including addiction, epilepsy, amyotrophic lateral sclerosis, Alzheimer's disease, schizophrenia, and mood disorders such as major depression and bipolar disorder.

Given the importance of glutamate in brain function and pathology, compounds that affect glutamatergic transmission potentially have broad applications in neurology and psychiatry. Drugs that affect glutamate receptor subtypes such as NMDA, kainate, and

AMPA—all of which are types of ionotropic receptors—have been eagerly pursued as potential treatments for conditions ranging from epilepsy to schizophrenia to anxiety. Glutamate binding to ionotropic receptors opens channels in neuronal membranes to permit the flow of ions with a resulting fast excitation of the neuron. While the fast excitatory actions of drugs affecting ionotropic glutamate receptors might have therapeutic benefit, they are also often associated with side effects and safety concerns. Generally, the



Hodge Lab (Left to Right): Front Row: Joyce Besheer, Ph.D., Mary Beth Wilkie, Clyde Hodge, Ph.D., Marina Spanos, Sara Faccidomo, Ph.D. Top Row: Amanda Sharko, Rebekah Stevenson, Jennie Hillman.

theoretical promise of drugs targeting ionotropic glutamate receptors has not yet been realized in clinical practice.

Dr. Clyde Hodge, Professor in the Department of Psychiatry and the Bowles Center for Alcohol Studies at UNC, is investigating a new and potentially more beneficial way of targeting the glutamate system. Hodge's laboratory works to discover neural

circuits and molecular mechanisms that mediate the rewarding and pleasurable effects of alcohol and uses this understanding to identify and validate potential treatments for alcoholism. Glutamate has been implicated in alcoholism like many other neuropsychiatric conditions, although the precise nature of glutamate's involvement is only beginning to be understood. Hodge's quest to understand the mechanism of alcohol's effects in the brain has led him to glutamate and to a metabotropic

glutamate receptor subtype known as the *mGluR5 receptor*. Metabotropic glutamate receptors differ from the traditionally targeted ionotropic receptors in that they mediate slower glutamate responses. Binding of glutamate to metabotropic receptors on the surfaces of neurons initiates a cascade of intracellular neurochemical events that occurs more slowly than the rapid changes in ion flux mediated by ionotropic glutamate receptors. In a sense,

drugs targeting metabotropic receptors are gentler modulators of glutamate function than drugs that target ionotropic receptors.

In one series of experiments, Hodge and his colleagues investigated the effect of MPEP, a drug that blocks mGluR5 receptors and thereby prevents their activation by glutamate, on self-

Continued on next page



Clyde Hodge, Ph.D.

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Education and Training

Ph.D., Experimental Psychology and Behavioral Pharmacology, 1991; M.S., Experimental Psychology, 1989, Auburn University, Alabama; B.S., Psychology, University of Alabama, Birmingham, 1986.

Recent Publications

Hodge, CW, Miles, MF, Sharko, AC, Stevenson, RA, Hillman, JR, Lepoutre, V, Besheer, J, Schroeder, JP. The mGluR5 antagonist MPEP selectivity inhibits the onset and maintenance of ethanol self-administration in mice. *Psychopharmacology*, 183: 429-438, 2006.

Hodge, CW, Grant, KA, Becker, HC, Besheer, J, Crissman, AM, Platt, DM, Shannon, ES, Shelton, KL. Understanding how the brain perceives alcohol: neurobiological basis of ethanol discrimination. *Alcoholism Clinical and Experimental Research*, 30(2): 203-213, 2006.

Besheer, J, Lepoutre, V, Mole, B, **Hodge, CW**. GABA-A receptor regulation of voluntary ethanol drinking requires PKC epsilon. *Synapse*, 31, 60(6): 411-419, 2006.

Newton, PM, Kim, JA, McGeehan, AM, Paredes, JP, Chu, K, Wallace, MJ, Roberts, AJ, **Hodge, CW**, Messing, RO. Increased response to morphine in mice lacking protein kinase C epsilon. *Genes, Brain, and Behavior*, In Press.

Website

<http://www.med.unc.edu/alcohol/faculty/HodgeCW/Hodge.htm>

administration of alcohol in mice. The drug self-administration paradigm is a means of studying the rewarding effects of drugs. In this paradigm, animals are trained to make a response—to press a lever a certain number of times, for example—in order to obtain reinforcing substances such as water or alcohol. Hodge and his laboratory found that MPEP dose-dependently reduced responding for alcohol in mice that had been trained to lever press to obtain alcohol. This effect was specific to alcohol: MPEP did not affect responding for water or suppress locomotor activity generally. Moreover, this effect was specific to blockade of the mGluR5 receptor: drugs that affect other metabotropic glutamate receptors, the mGluR2/3 and mGluR1 receptors, did not affect lever-press responding for alcohol. These results suggest that mGluR5 receptors contribute to regulation of alcohol drinking, possibly by affecting the rewarding properties of alcohol. Blockade of the mGluR5 receptor with MPEP may have reduced the rewarding properties of alcohol as demonstrated by the MPEP-mediated reduction of alcohol-reinforced responding.

In another series of studies, Hodge and his laboratory showed that MPEP also reduced alcohol-reinforced responding in the alcohol-preferring (P) rat. P rats are bred for their high alcohol intake and have been used as a genetic model of alcoholism. In the P rat, MPEP, but not mGluR2/3 or mGluR1 antagonists, reduced alcohol-reinforced responding. MPEP also influenced responding for alcohol after a period of alcohol deprivation. In animals trained to respond for alcohol, periods of abstinence from alcohol are associated with increased responding for alcohol once it is reinstated, an effect known as the “deprivation effect.” The deprivation effect models relapse in human alcoholics, who often drink more than they normally would when they reinitiate drinking after a period of abstinence—when they “go off the wagon.” Hodge found that P rats given MPEP before alcohol deprivation sessions did not demonstrate the deprivation effect. However, the deprivation effect was observed in P rats given saline before alcohol deprivation sessions. Saline-treated rats self-administered more alcohol when it was reinstated after periods of

deprivation than they did before the deprivation periods. These results suggest that the mGluR5 receptor modulates both the maintenance of alcohol intake and the increases in alcohol intake associated with periods of abstinence.

In an important extension of this work, Hodge and Dr. Joyce Besheer, an Assistant Professor in the Department of Psychiatry and the Bowles Center for Alcohol Studies at UNC, have shown that the mGluR5 antagonist MPEP inhibits the discriminative stimulus (i.e., subjective) effects of alcohol in rats. Using a combined behavioral, pharmacological, and anatomical approach, the team showed that this effect of MPEP may be mediated through an interaction with the brain’s primary inhibitory transmitter system: GABA_A receptors. Hodge notes that “These data suggest that mGluR5 may regulate how the brain perceives alcohol by altering GABA neurotransmission in specific brain regions.”

Metabotropic glutamate receptors such as mGluR5 modulate glutamate function by causing a cascade of intracellular neurochemical events that ultimately results in a change in neuronal excitability. Hodge’s work currently focuses on elucidating the specific molecular events involved in this cascade of intracellular responses. One of the intracellular effects of stimulation of the mGluR5 receptor is activation of an enzyme known as protein kinase C-epsilon. Hodge and his colleagues have demonstrated the importance of protein kinase C-epsilon in alcohol-reinforced responding by showing that the effect of MPEP on alcohol self-administration depends on the presence of protein kinase C-epsilon. MPEP, which dose-dependently reduces consumption of alcohol in normal mice, did not reduce consumption in mice bred to lack protein kinase C-epsilon. Ongoing studies are elucidating additional molecular components of the mGluR5 intracellular signaling pathway that show adaptive changes in response to chronic alcohol self-administration (Figure). In ongoing work, Hodge is also assessing the degree to which metabotropic glutamate receptor regulation of alcohol self-administration is specific to particular brain regions. “Our overall goal,”

continued on next page



The Director's Column

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

The interaction of ethanol and glutamate neurotransmission has been an exciting area of research for a little more than a decade. Soon after the discovery of the glutamate N-methyl-D-aspartate (NMDA) receptor, it was discovered that ethanol inhibited this key receptor. Widespread studies investigated ethanol-NMDA interactions, including many that supported a significant component of ethanol's effects being related to alterations in glutamate transmission. For years, one conundrum was the variations in ethanol's regional brain effects on NMDA-glutamate transmission and how behavioral responses related to the ability of ethanol to inhibit NMDA receptors.

Recent understanding of synaptic efficacy has indicated that multiple proteins cluster with synaptic NMDA-glutamate receptors regulating the opening of the NMDA receptor ion channel in addition to other signaling synaptic elements. Together, these proteins regulate excitatory synaptic efficacy. Within the glutamate

synapse, metabotropic glutamate receptors and specific protein kinases regulate synaptic excitation, responsiveness and the shape of the postsynaptic element. Interestingly, the agonist NMDA does not activate metabotropic or other glutamate synaptic regulators. Clyde Hodge recognized that glutamate synaptic elements were important to ethanol's actions and noted that mGluR5 metabotropic glutamate receptors were uniquely expressed in mesolimbic brain regions important for alcohol craving and motivation.

The discovery that mGluR5 receptors play a key role in regulating alcohol seeking behaviors is particularly exciting since mGluR5 receptors are localized to brain regions that mediate drug liking, craving and consummatory behavior. These receptors do not impact other important brain regions where learning and synaptic plasticity play a key role. Clyde Hodge's research on the role of mGluR5 receptors in addiction are being extended to other drugs of abuse, particularly nicotine, which is often abused in conjunction with alcohol. Glutamate synaptic transmission is clearly a key element of drug dependence. The selective modulation of mesolimbic regions involved in driving drug seeking and craving through mGluR5 inhibitors opens a new and exciting area of discovery that could contribute to better treatments for those with alcohol dependence. ■

continued from previous page

Hodge says, "is to identify molecular and cellular adaptations that occur in the brain after long-term voluntary alcohol drinking, and then to determine if these adaptive changes regulate maladaptive behaviors, such as relapse. The mGluR5 pathway appears to be a target of self-administered ethanol that also regulates drug taking behavior. We are excited about this bidirectional linkage."

Hodge is keenly interested in potential clinical applications of his research. "We use animal models to study the neural mechanisms that underlie alcohol drinking with the hope that we can use the knowledge we gain to better target potential pharmacotherapies," Hodge says. "Our work with the mGluR5 receptor exemplifies this approach. Much past research in the field focused on involvement of ionotropic glutamate receptors in the neurobiological effects of alcohol. However, the clinical usefulness of drugs affecting ionotropic glutamate receptors may be limited. Targeting metabotropic glutamate receptors appears to be a more promising approach; these receptors are quickly emerging as important therapeutic targets in numerous areas of neuropathology. We hope that our work advances understanding of metabotropic glutamate receptor regulation on alcohol reinforcement and provides important information for the development of pharmacotherapies for alcoholism." ■

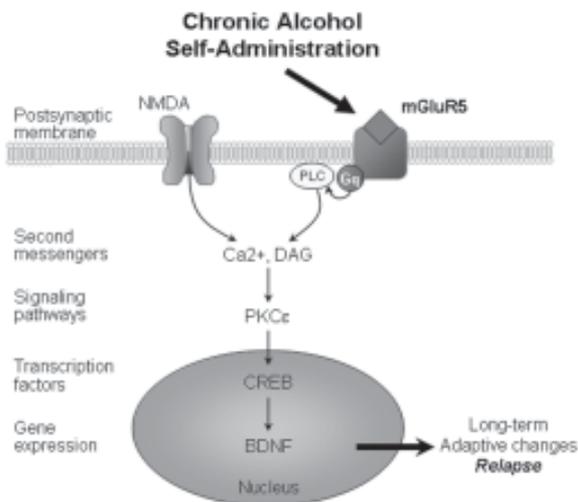


Figure: Schematic showing how chronic alcohol self-administration may modulate mGluR5, which in turn can change glutamate cell signaling pathways that influence gene expression and long-term behavioral changes.

**A. Leslie Morrow Delivers
American Psychiatric Association
Frontiers of Science Lecture
"High on Neuroactive Steroids:
Mechanisms and Therapeutic Relevance"
May 24, 2006**

Alcohol Center Founder John A. Ewing: 1923-2006

Dr. John A. Ewing, founder of the UNC Center for Alcohol Studies, died June 3 at the age of 83 at his home in Wilmington, N.C.

An English-trained psychiatrist whose parents struggled with alcohol, Ewing joined the state psychiatric hospital in Butner, N.C., in 1951. Dr. George Ham, Chair of the UNC Department of Psychiatry, noted Ewing's interest in alcoholism and recruited him to Chapel Hill a few years later to direct training, treatment, and research in alcoholism and drug dependency.

In the late 1960's, Sam Johnson, an attorney and member of the NC House of Representatives, wrote an article about how we control alcohol but do not understand much about alcoholism. UNC President Bill Friday, having read Sam

Johnson's article, called Ewing, introduced him to NC Senator Hargrove "Skipper" Bowles, and organized a bill to fund alcohol research that first formed the "Alcoholism Research Authority."

Throughout the 1970's, Ewing organized researchers at UNC to treat alcoholism as a disease. He also promoted use of a diagnostic tool he developed, the CAGE. In a seminal research paper, "Detecting Alcoholism: The Cage Questionnaire" (JAMA, 252:1905-7, 1984), Dr. Ewing described four simple questions that focused on Cutting back, Annoyance by criticism, Guilty feelings and Eye-openers (forming the CAGE acronym). This questionnaire helps physicians remember questions that do not prompt denial responses but do identify problem drinkers.

The CAGE is still being used around the world and has prompted numerous new versions with acronyms like AUDIT and MAST. The concept of a simple diagnostic tool to identify patients with alcohol use disorder was a unique idea at the time that continues to help physicians today.

In 1984, Dr. Ewing left UNC and moved to Wilmington where he had a clinical practice. However, the UNC group Ewing had organized remained active. In time, the Center for Alcohol Studies found housing in a mobile home, received state support, and in 1994 moved into its own Hargrove Skipper Bowles building.

Dr. Ewing promoted alcoholism as a disease that should be treated medically, and he advocated for research to better understand the causes, prevention and treatment of alcoholism and alcohol abuse. His likeness graces a "Founding Director" plaque in the lobby of the Center. He will be remembered by all as a giant in the field of alcoholism and dependency research. ■



The Bowles Center for Alcohol Studies

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To become involved in our mission, call Elizabeth Thomas at (919) 966-4977 or email ethomas@med.unc.edu.

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 966-6039 or (888) 457-7457.

www.med.unc.edu/alcohol

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