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.

ISSN 0738-6567 Volume 14, Number 4, December 2003

Morrow Lab Finds New Mechanisms of Alcohol Dependence

Alcohol dependence is a pervasive problem in the United States. Data from a nationally representative survey show that, among employed US adults, more than 10% of men and 4% of women are dependent upon alcohol. The Diagnostic and Statistical Manual of Mental Disorders, 4th edition (DSM-IV), which is the manual psychiatrists use as a guide to diagnosing mental disorders, characterizes alcohol dependence by criteria including tolerance (i.e., increased drinking to achieve the same effect), alcohol withdrawal signs, drinking more than intended, and alcohol-related impairment in social or work activities. As these criteria reveal, alcohol dependence is a multifaceted disorder with physical, psychological, and behavioral manifestations that are related in part to the behavioral response to alcohol.

Dr. A. Leslie Morrow and her laboratory at the University of North Carolina's Skipper Bowles Center for Alcohol Studies devote their efforts to elucidating the molecular underpinnings of alcohol dependence. By understanding the mechanisms underlying the various aspects of alcohol dependence, they hope to pave the way for the development of pharmacologic interventions for the treatment of alcoholism. Their work focuses on $GABA_A$ receptor gated chloride (Cl^-) ion channels that, when acted upon by substances such as neurotransmitters, control the activity of nerve cells in the brain. It has long been known that alcohol influences the function of $GABA_A$ receptors and that the effects of alcohol on GABAergic neurotransmission contribute to various behavioral responses to alcohol (e.g., sedation, cognitive dysfunction) occurring during alcohol use. The precise means by which alcohol alters $GABA_A$ receptors has not been understood until recently—thanks largely to the efforts of a handful of researchers, including Morrow and her laboratory colleagues.

The Morrow Reasearch Team: *(Left to Right) Rahul Khisti, Ph.D., A. Leslie Morrow, Ph.D. (P.I.), Sandeep Kumar, M.D., Shannon Penland, Mary Beth Wilkie, Todd O'Buckley, Rebekah Fleming, Sandra O'Buckley, Mary Berghaus and Brooke Schildwachter.*

Morrow's work reveals that the effects of chronic alcohol exposure on $GABA_A$ receptors are as multifaceted as the physical and behavioral manifestations of alcohol dependence itself. She and her colleagues have identified several ways that alcohol may interact with GABA (one of the brain chemicals that binds to $GABA_A$ receptors) and $GABA_A$ receptors to cause phenomena such as tolerance and alcohol withdrawal. For example, work by Morrow and others shows that ethanol dependence is associated with altered function of $GABA_A$ receptors, including reduced sensitivity to the neurotransmitter GABA as well as alcohol and benzodiazepines such as Valium®. Additionally, withdrawal symptoms reflecting physical dependence can be related to loss of GABA-associated neuronal inhibition with resultant excessive excitation when alcohol is no longer present.

Morrow's more recent work has focused partly on the microstructure and function of the $GABA_A$ receptors. Each $GABA_A$ receptor is composed of several subunits. Over the last fifteen years, Morrow's group showed that chronic exposure to alcohol alters the expression of genes that code for these subunits throughout brain. With altered genomic activity, the numbers of specific $GABA_A$ receptor subunits can increase or decrease. The changes in $GABA_A$ receptor subunits can alter the functioning of $GABA_A$ receptors and, correspondingly, can alter behaviors mediated by $GABA_A$ receptors. For example, chronic exposure of nerve cells containing $GABA_A$ receptors to alcohol changes the numbers of specific $GABA_A$ receptor subunits in virtually every brain region, including the cerebral cortex, hippocampus, amygdala, and cerebellum. The regulation of various $GABA_A$ receptor subunits by ethanol differs across regions of the brain. Some of these changes have been closely linked to ethanol tolerance as well as withdrawal symptoms such as anxiety and seizures. These negative symptoms of ethanol dependence are also known to increase drinking.

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A. Leslie Morrow, Ph.D.

Associate Director and Professor, Bowles Center for Alcohol Studies; **Professor**, Departments of Pharmacology and Psychiatry

Education

Ph.D., 1985, UC - San Diego; Neuroscience
B.S., 1977, UC - Davis; Major in Psychobiology

Recent Publications

Grobin AC, Heenan EJ, Lieberman JA, **Morrow AL** (2003). Perinatal neurosteroid levels influence GABAergic interneuron localization in adult rat prefrontal cortex. Journal of Neuroscience 23(5): 1832-1839.

Kralic JE, Wheeler M, Renzi K, Ferguson C, O'Buckley TK, Grobin AC, **Morrow AL**, Homanics GE (2003). Deletion of $GABA_A$ receptor α1 subunit-containing receptors alters responses to ethanol and other anesthetics. J. Pharmacol. Exp. Ther., 305 (2): 600-607.

Kumar S, Kralic JE, O'Buckley TK, Grobin AC, **Morrow AL** (2003). Chronic ethanol consumption enhances internalization of α1 subunit-containing $GABA_A$ receptors in cerebral cortex. J. Neurochem 86: 700-708.

Khisti RT, VanDoren MJ, O'Buckley TK, **Morrow AL** (2003). Neuroactive steroid 3α-hydroxy-5α-pregnan-20-one modulates ethanol-induced loss of righting reflex in rats. Brain Research 980:255-265.

Khisti RT, Kumar S, **Morrow AL** (2003). Ethanol rapidly induces steroidogenic acute regulatory protein expression and translocation in rat adrenal gland. Eur. J. Pharm 473: 225-227.

Morrow, AL, Khisti, RT, Tokunaga, S, McDaniel, JR, Matthews, DB (2003). GABAergic neuroactive steroids modulate selective ethanol actions: Mechanisms and significance. In: *Neurosteroid Effects in the Central Nervous System: The Role of the $GABA_A$ Receptor,* Smith, S.H. (Ed.) CRC Press LLC, Miami, pp. 219-245.

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

Research partially funded by NIAAA.

Alcohol may also affect $GABA_A$ receptors through its interaction with other, non-$GABA_A$ receptors. Multiple receptor types reside on the surfaces of nerve cells. Both the $GABA_A$ receptor and the NMDA receptor, for example, frequently coexist on nerve cells. When a neurotransmitter or hormone contacts either of these receptor types, a cascade of intracellular responses is initiated. The intracellular signaling pathways activated by different receptors can overlap such that activation of one type of receptor influences the function of a signaling pathway associated with a different receptor. Morrow and her colleagues found that MK-801, a drug that blocks NMDA receptors but does not affect $GABA_A$ receptors, caused changes in numbers of specific $GABA_A$ receptor subunits in the hippocampus, a brain region involved in learning and memory. The effect of MK-801 on $GABA_A$ receptors was determined to be mediated by cross-talk inside the nerve cells between the signaling pathway associated with the NMDA receptor and that associated with the $GABA_A$ receptor. Alcohol is known to inhibit NMDA receptor function, and discrimination studies indicate that alcohol is often perceived to be an NMDA antagonist (like MK-801). Together, these findings raise the intriguing questions of whether the mechanism of alcohol-induced changes in $GABA_A$ subunits could be secondary to effects on NMDA and whether NMDA receptor drugs induce changes in $GABA_A$ receptor subunits that can alter alcohol tolerance or dependence.

Alcohol can also affect $GABA_A$ receptors through non-genomic mechanisms. For example, alcohol can alter the function of $GABA_A$ receptors by modifying their location. To be functional in neurotransmission (i.e., in receiving and transmitting electrochemical signals from one nerve cell to another), $GABA_A$ receptors must be localized on the surface of nerve cells so that they are exposed to neurotransmitters. Chronic exposure to alcohol can cause specific $GABA_A$ receptors to be internalized by the nerve cell while other $GABA_A$ receptor subtypes accumulate on the cell surface. The internalization of $GABA_A$ receptors renders them unable to respond normally to extracellular signals and the responses of these cells have different properties. Morrow notes that behavioral and physical manifestations of alcohol dependence arguably arise from such changes in the ability of the $GABA_A$ receptors to respond normally to chemical signals.

Besides affecting $GABA_A$ receptor function through changes in its genes and localization of receptors, alcohol can indi-

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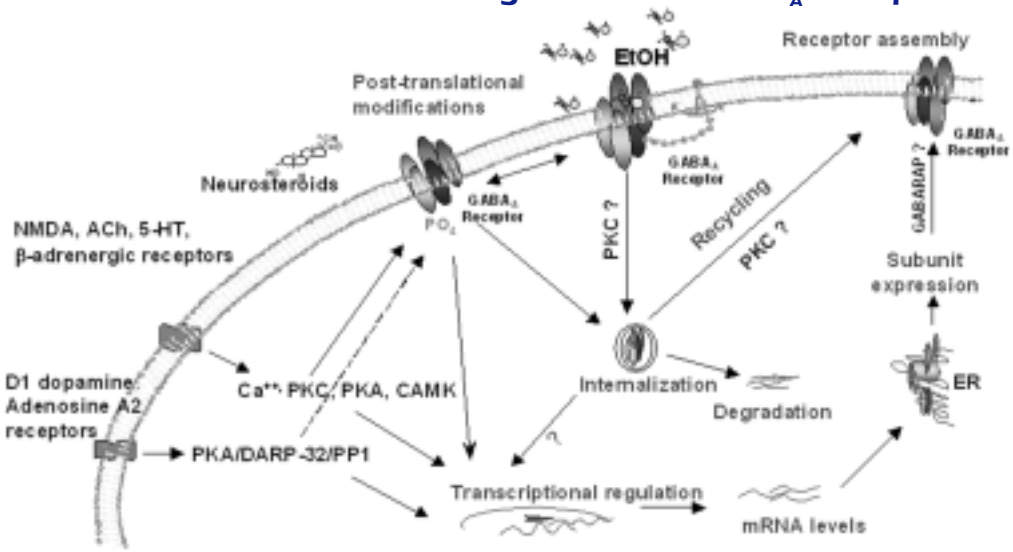
Mechanisms of Ethanol Regulation of $GABA_A$ Receptors



Potential mechanisms of $GABA_A$ receptor regulation following chronic ethanol administration. Chronic ethanol administration results in *altered mRNA and peptide levels* of various $GABA_A$ receptor subunits, $GABA_A$ receptor α1 subunit *internalization,* and decreased levels of *phosphorylated* α1 subunits in the synaptic fraction. *Neurosteroids* alter the sensitivity of $GABA_A$ receptors and regulate their expression *in vivo. NMDA, mAch, serotonin, D1 dopamine and adenosine A2 receptors* are modulated by ethanol and can modulate $GABA_A$ receptor function via various intracellular signaling proteins. The signaling proteins involved in these actions include PKC, PKA, CAMK, Ca^{++}, and DARP-32.

The Director's Column

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

Leslie Morrow's work on the $GABA_A$ receptors, the brain and behavioral responses to alcohol are writing the road map and paving the road to our understanding of the mechanisms of tolerance to alcohol. $GABA_A$ receptors contribute to anxiety, sedation, motor (balance and coordination) dysfunction and many other behaviors key to alcohol's effects. Many of my smartest colleagues believe that tolerance and the dynamic rapid tolerance that occurs as the blood alcohol level rises is among the most important determinants of risk for development of alcohol dependence. There are genetic, environmental, and learned aspects to tolerance, each of which could involve $GABA_A$ receptors. Genetic studies have established low tolerance or the plastic ability to rapidly become tolerant to alcohol as being a major risk factor for alcohol dependence. The complex ways that alcohol can alter $GABA_A$ receptors will help us understand the antecedents and sequelae that lead to alcohol dependence as well as many other processes important for a healthy mind and brain. Leslie Morrow is cutting the road through this complex landscape looking to find the key place to use this knowledge to benefit mankind. It will happen, we just do not know when.

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rectly affect $GABA_A$ receptor function by altering levels of steroids that interact with $GABA_A$ receptors. The steroid allopregnanolone, for example, is one of the most potent known modulators of $GABA_A$ receptor function and, Morrow reasoned, a likely candidate for mediating some of the effects of alcohol on behavior. In support of this possibility, Morrow and her laboratory found that rats injected with an intoxicating dose of alcohol exhibited ~700% increases of allopregnanolone in the cerebral cortex, a brain region important in the sedative and cognitive effects of alcohol. However, in tolerant and dependent rats, the ability of ethanol to increase brain allopregnanolone levels is diminished. This change may account for diminished responses to alcohol that often leads to excess drinking.

"No mechanism in isolation can explain the complex, multifaceted disease that is alcoholism," says Morrow. "Our research shows that multiple mechanisms are involved in alcohol effects at $GABA_A$ receptors, which is just one of several receptor types that alcohol influences. We've seen that alcohol can cause genomically mediated changes in $GABA_A$ receptor subunits as well as non-genomically mediated changes in $GABA_A$ receptor structure and location. Alcohol can also cause changes in the levels of steroids that modulate the function of $GABA_A$ receptors. These effects are proving to be important in explaining phenomena such as tolerance and alcohol withdrawal—key aspects of alcohol dependence."

Arthur Cederbaum Receives 2003 Ronald G. Thurman Award

L to R: Drs. A. Leslie Morrow, Arthur Cederbaum and Fulton Crews

Arthur Cederbaum, Ph.D., received the 2003 Ronald G. Thurman Lectureship Award on September 23 to acknowledge his contribution to our knowledge of alcohol and liver function. Dr. Cederbaum presented a lecture, "CYP2E1: Biochemistry, toxicology and regulation in liver cells," and met with faculty to share knowledge and new ideas. Dr. Cederbaum is a Professor of Pharmacology and Biological Chemistry at Mount Sinai School of Medicine, New York.

Gwyther Honored with 2003 Fuller Award

Dr. Robert E. Gwyther, Professor and Center for Alcohol Studies member at UNC, received the 2003 H. Fleming Fuller Award on Nov. 21 at the UNC Health Care board of directors' annual banquet. Given annually in memory of Fuller, a Kinston physician and founding member of the UNC Hospitals board who died in 1986, the award recognizes doctors who demonstrate compassionate patient care and excellence in teaching and community service.

Gwyther has had a full-scope family practice at UNC since 1978 and has been delivering babies at UNC longer than any other faculty member. He also has a special interest and expertise in the treatment and prevention of alcoholism and drug abuse. Dr. Gwyther organized the 2003 CAS Education Meeting: "Understanding and Treating the Spectrum of Alcohol and Substance Abuse Problems"

He currently is chair of the NCAFP's board of directors. Gwyther has also served on the Governor's Institute on Alcoholism and Substance Abuse and the North Carolina Physicians Health and Effectiveness Committee.

Governor Michael Easley appoints Bowles Center member Bill Renn to the North Carolina Substance Abuse Advisory Council

Bill Renn, LCSW, MSW, Director of the UNC-Alcohol and Substance Abuse Treatment Clinic and Assistant Professor of Psychiatry was appointed to a four- year term to the council which makes recommendations to the Secretary of the NC Department of Corrections on substance abuse programs, continuity of care, and community treatment programs.

Crews Receives APNC Norbert L. Kelly Award

Addictions Professionals of North Carolina (APNC) presented the 2003 Norbert L. Kelly Award to Dr. Fulton T. Crews, Director of the Skipper Bowles Center for Alcohol Studies at the University of North Carolina at Chapel Hill. Below is the award text presented to Dr. Crews:

L to R:Phil Mooring - President, APNC; Dr. Fulton T. Crews - Director, CAS; Anthony Mulvihill, Executive Director, ADCNC.

The foundation of the modern recovery movement is the understanding that alcoholism/addiction is a biologically based disease, not willful or "sinful" behavior. In North Carolina the wellspring of the modern understanding of addiction as a brain disease is the Skipper Bowles Center for Alcohol Studies at UNC/Chapel Hill. The driving force of the Bowles Center is its Director, Fulton Crews.

Biological science has its own language. No one has worked harder to make the language of biological science intelligible to the layman, and to the front line addiction professional, than has Dr. Crews. He has reached out to make the latest and best scientific information on the brain disease of addiction available to us all. He has accomplished this through his consistently brilliant lectures given throughout the state – and through his active service on Boards of Directors of front-line organizations such as Freedom House, the NC Governor's Institute, Pavillon International and the Alcohol/Drug Council of North Carolina.

As a respected member of the Academic Community (Professor of Curriculum in Toxicology & Professor of Pharmacology and Psychiatry at UNC/Chapel Hill; Courtesy Professor of Pharmacology, University of Florida) and a widely sought-after national lecturer, Dr. Crews also conveys the practical insights of our front-line profession to the cloistered halls of academia.

The alcohol and drug field is bedeviled by misinformation and disinformation. Fulton Crews, more than any other person in North Carolina, is working to produce the scientific facts related to addiction and to make those facts available and intelligible to the public and academic world. He is doing terribly important work and APNC and the entire Field is extremely grateful to him.

APNC is privileged to convey the Norbert L. Kelly Award, its highest award for distinguished service to those who suffer from addiction, upon Fulton T. Crews, Ph.D., this 23rd day of October, 2003, in Southern Pines, North Carolina.

The Bowles Center for Alcohol Studies

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To become involved in our mission, call Elizabeth Amend at (919) 843-6204 or email amend@unc.edu.

For treatment information call UNC Health Care's Alcohol and Substance Abuse Program at (919) 402-1644.

www.med.unc.edu/alcohol

Center Line, Vol. 14 No. 4 *Published quarterly to bring greater understanding of alcoholism research and the Center's mission.*
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