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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Morrow Lab Identifies Mechanisms of Alcohol Sensitivity: A Key Mediator of Risk for Alcohol Dependence

Who is most likely to become an alcoholic—the person highly susceptible to its mind-altering and incoordinating effects or the one who seems impervious to them? Counterintuitively, the one who seems impervious to the acute effects of alcohol is the one most likely to develop alcoholism, all other things being equal. In fact, low sensitivity to alcohol is among the best predictors of alcoholism and appears to be a significant mediator of risk for becoming an alcoholic. In a classic study that followed a group of more than 200 sons of alcoholics and a comparison group of individuals who were sons of non-alcoholics but were otherwise similar to the first group, those with low sensitivity to alcohol at the age of 20 years were four times more likely to develop alcoholism later in life than more alcohol-sensitive individuals (Schuckit MA. *Am J Psychiatry* 1994;151:184-189). Alcohol-impervious individuals, those with an ability to drink heavily, were more likely than alcohol-sensitive ones to become alcoholics, regardless of whether their fathers were alcoholics. Given the strong association between low alcohol sensitivity and risk for alcoholism, elucidation of mechanisms of sensitivity to alcohol is a hot topic among neuroscientists and alcohol researchers. With an understanding of its mechanisms, alcohol sensitivity—and therefore risk for alcoholism—might be amenable to modification.

Dr. A. Leslie Morrow and her laboratory at the University of North Carolina Bowles Center for Alcohol Studies have significantly advanced understanding of the mechanisms of alcohol sensitivity with their research on $GABA_A$ receptors and neuroactive steroids. $GABA_A$ receptors are protein complexes that span the membranes of brain cells. When acted upon by substances such as neurotransmitters and hormones, $GABA_A$ receptors alter the electrical activity of brain cells by opening or closing cell-membrane-spanning channels that allow passage of negatively charged chloride ions. Neuroactive steroids, which are produced by various glands (e.g., adrenals) and organs (e.g., gonads, brain), are among the substances that bind to sites on $GABA_A$ receptors to modulate their ability to inhibit neurotransmission.

Morrow Lab (Left to Right): Front Row: Eric Zimmerman, Kevin Boyd, Todd O'Buckley. Middle Row: Anthony Blount, A. Leslie Morrow, Ph.D., Sandeep Kumar, M.D. Top Row: Patrizia Porcu, Ph.D., Sarah Alward, Marvin Lai.

Scientists have long recognized that $GABA_A$ receptors are important in mediating the anxiolytic, sedative, anticonvulsant, and cognitive-impairing effects of alcohol; however, the specific mechanisms by which alcohol produces such effects have remained largely a mystery. The inability to identify clear, direct actions of alcohol on $GABA_A$ receptors has stymied researchers: how can we explain alcohol's modulation of $GABA_A$-receptor-mediated functions if not by a direct action of alcohol on the receptor? New data from Morrow's lab suggest that the answer to this question partly lies in the ability of alcohol to affect $GABA_A$ receptor phosphorylation. Phosphorylation, or the addition of phosphates to a protein, throws a molecular switch that activates or deactivates the receptor protein and can thereby change the function of receptors. Phosphorylation occurs through the action of various enzymes including *protein kinase C* (PKC). Normally, PKC-mediated phosphorylation reduces $GABA_A$ receptor function. Morrow and her colleagues found that acute administration of

Continued on next page

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Affiliations

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Education and Training

Post-doctoral training in molecular neuropharmacology, National Institute of Mental Health, Bethesda, MD, 1988; Ph.D., Neuroscience, University of California, San Diego, 1985; B.A., Psychobiology, University of California, Davis, 1977.

Recent Publications

Kumar, S, Lane, BM, **Morrow, AL**. Differential effects of systemic ethanol administration on PKCε, γ and β isoform expression, translocation to membranes and target phosphorylation: Reveral by chronic ethanol exposure. J. Pharmacol. Exp. Ther., 319 (3): 1366-75 (2006).

Porcu, P, Grant, KA, Green, HL, Rogers, LSM, **Morrow, AL**. Hypothalamic-pituitary-adrenal axis and ethanol modulation of deoxycorticosterone levels in Cynomolgus monkeys. Psychopharmacology, 186: 293-301 (2006).

Kumar, S, Khisti, RT, **Morrow, AL**. Regulation of native $GABA_A$ receptors by PKC and protein phosphatase activity. Psychopharmacology, 183:241-247 (2005).

Pierucci-Lagha, A, Covault, J, Feinn, R, Nellissery, M, Hernandez-Avila, C, Oncken, C, **Morrow, AL**, Kranzler, HR. GABRA2 alleles moderate the subjective effects of alcohol, which are attenuated by finasteride. Neuropsychopharmacology, 30: 1193-1203 (2005).

Website

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

alcohol to rats reduces PKC-mediated phosphorylation of $GABA_A$ receptors. Given that PKC-mediated $GABA_A$ receptor phosphorylation normally reduces $GABA_A$ receptor function, the putative net effect of alcohol's reduction of phosphorylation is enhancement of $GABA_A$ receptor-mediated inhibition. Morrow's lab also found that chronic administration of alcohol is associated with tolerance to alcohol's effect on PKC-mediated phosphorylation: with chronic use, alcohol loses its ability to alter PKC expression and activity. These results suggest a crucial role of PKC-mediated phosphorylation in the action of alcohol at $GABA_A$ receptors. Some of these data are described in a paper that was published recently in *The Journal of Pharmacology and Experimental Therapeutics*.

PKC exists in several forms in neurons, including PKCε, PKCβ, and PKCγ. In a series of experiments, the Morrow lab demonstrated that alcohol has specific, selective effects on various forms of PKC depending on whether alcohol is administered acutely or chronically. Acute administration of alcohol affects the production, intracellular localization, and phosphorylation of PKC enzymes. For example, in a study of acute alcohol administration in rats, alcohol affected production of some forms of PKC but did not affect others. Acute alcohol administration also affected the cellular location of PKC enzymes in the brain's cerebral cortex: PKCε was increased in the intracellular fluid but not in nerve cell membranes.

Prolonged administration of alcohol changes the way that PKC enzymes interact with $GABA_A$ receptors. In one study, Morrow and her colleagues showed that chronic administration of alcohol markedly increased the association of PKCγ with a particular subtype of the $GABA_A$ receptors that contain α4 subunit proteins. At the same time, chronic administration of alcohol increased the expression of the α4 subunits in the membranes of brain cells. This pattern of results suggests the possibility that PKCγ influences the membrane expression of this important $GABA_A$ receptor subtype. The results are consistent with the possibility that alcohol-associated changes in PKCγ affect cell signaling involving this $GABA_A$ receptor by influencing its expression on the cell surface, where it binds neurotransmitter.

Other experiments by Morrow and her colleagues reveal exciting parallels between alcohol effects on $GABA_A$ receptor phosphorylation and alcohol effects on neuroactive steroids that bind to sites on $GABA_A$ receptors. Acute administration of alcohol markedly increases levels of specific neuroactive steroids in plasma and most brain areas. The increase in neuroactive steroid levels enhances GABAergic neurotransmission. Furthermore, blocking the effect of ethanol on neuroactive steroid levels reduces many of ethanol's effects, including its relaxing, anticonvulsant, sedating, and cognitive-impairing effects. With chronic administration, the effect of alcohol on levels of neuroactive steroids—like its effect on $GABA_A$-receptor-modulating PKC activity—is reduced.

"These differences in the GABAergic effects of acute and chronic alcohol might hold a key to explaining differences in alcohol sensitivity," said Morrow. "Alcohol-induced enhancement of GABAergic neurotransmission during acute alcohol administration might correspond to an alcohol-sensitive state associated with a low risk of excessive drinking. With chronic consumption of alcohol, this sensitivity is lost such that an increase in consumption is required to achieve the desired effect. Alcohol's effect on PKC and $GABA_A$ receptor phosphorylation is a cellular mechanism of alcohol sensitivity, while alcohol's effect on neuroactive steroid levels is a systemic mechanism." **(Figure)**

In the experiments described above, chronic alcohol administration was responsible for the blunting of GABAergic responses and the corresponding reduction in alcohol sensitivity. Other factors besides chronic administration or consumption could contribute to a blunted GABAergic response and a reduction in alcohol sensitivity. For example, chronic stress suppresses the production of some neuroactive steroids and could thereby contribute to reduced alcohol sensitivity.

continued on next page

The Director's Column

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

Neurosteroids: Unique Signaling Molecules Important for Harmony

What a pleasure to write about the cutting edge work of Dr. Leslie Morrow. $GABA_A$ receptors are the major proteins responsible for the signaling of GABA, a critical inhibitory transmitter that is the major brake within the brain. The brain, in large part, works by selective inhibition. GABA regulates many intricacies of brain function that require selective inhibition. Examples of selective inhibition include focusing on a conversation in the presence of background noise or having that noise become the annoying focus of your attention. The ability to focus often depends on GABA inhibition of specific brain pathways.

GABA is very abundant and common across the brain, and if it isn't working properly, it has the potential to cause seizures. But more subtly, it controls anxiety, mood and muscle tone, key elements of relaxation and health. Morrow's lab has studied the unique configurations of $GABA_A$ subunits (each a gene) that make different subtypes of $GABA_A$ receptors across the brain. Further, she has found adaptive changes in the expression of types of complexes within neurons during chronic ethanol treatment and withdrawal. However, most exciting is Morrow's recent discovery that ethanol regulates which $GABA_A$ receptor complexes become "active" cell surface receptors – an effect that appears to be key to understanding GABA neurotransmission. Several findings suggest that GABA is a central component of alcohol's actions, and discoveries are of paramount importance for understanding GABA transmission and how it is altered by alcohol dependence. This work is nicely presented in the cover article. However, Morrow's discoveries go far beyond alcoholism.

Anxiety and mood are key components of multiple mental disorders. Our mood and anxiety can make the glass half full or half empty. Most mental disorders occur much more often than expected by chance in alcohol abusing and alcohol dependent individuals, with dependent individuals even more likely than abusers to have mental disorders. Dysfunctional feelings can be crippling, and GABA contributes to those processes. The role of GABA in mental disease is likely to involve endogenous neurosteroids altering GABA in ways that make the brain dysfunctional. Loss of inhibitions and loss of control could involve loss of selectivity in GABA functions in the brain.

Morrow's new discoveries provide an entirely new process regulating this critical component of brain function. Her work may lead to new therapies for alcoholism and many other mental afflictions. It continues to excite scientists across the world. We do all we can at UNC to support her continued efforts to understand mental disease and innovative new ideas on how it might be treated. ■

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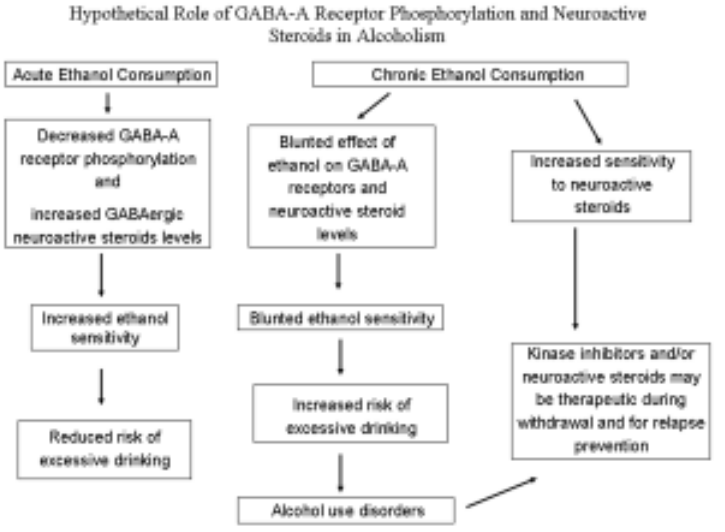
Figure



In addition, genetic differences in steroid production or GABAergic function could explain differences in alcohol sensitivity among individuals.

Morrow notes that this research has important implications for treating alcohol-dependent individuals. If low sensitivity to alcohol increases risk of excessive drinking, then restoration of alcohol sensitivity might be therapeutically useful. Morrow and colleagues' research suggests the possibility that administration of neuroactive steroid analogs or specific kinase inhibitors could enhance alcohol sensitivity and thereby reduce the risk of excessive drinking. To provide a foundation for exploring these possibilities, Morrow has begun to extend her work on mechanisms of alcohol sensitivity from animal models to humans. She speaks enthusiastically of the future: "We are finding some provocative similarities between the animal work and the human work. However, because humans and nonprimates differ in key ways—for example, in the specific GABAergic neuroactive steroids that they produce—we also expect to find some differences. We have discovered potential new targets for alcoholism treatment, but there is much more to learn." ■

Correction: In September's back-cover article, we referred to the late John A. Ewing as "An English-trained psychiatrist whose parents struggled with alcohol." The sentence should have read "whose patients struggled with alcohol." We sincerely regret this error.

Yedy Israel Receives Thurman Lectureship Award

The 2006 Ronald G. Thurman Lectureship Award was presented to Yedy Israel, Ph.D., on October 9 at the University of North Carolina at Chapel Hill. Well known for leading the field in alcoholism research, Israel is a Professor of Pharmacology at the University of Chile in Santiago and an Adjunct Professor of Pathology and Cell Biology at Thomas Jefferson University in Philadelphia.

Over his long career, Israel has been honored with numerous awards including a MERIT award from the National Institutes of Health and the Jellinek International Memorial Fund Award. He has served as scientific co-director for the NIAAA Center on Alcoholism at Thomas Jefferson University, as well as director of the Ph.D. Program in Biochemistry at the University of Chile.

Dr. Fulton Crews (left) with Ximena Eidelstein Israel, Dr. Yedy Israel, and Dr. A. Leslie Morrow.

"I can't think of a better person to receive the 2006 Thurman Award," said Bowles Center for Alcohol Studies Director Fulton Crews. "Yedy demonstrates the same charisma, depth, breadth and academic excellence as the late Ronald Thurman. Over the years, Dr. Israel has made important breakthroughs in alcohol metabolism, alcohol liver disease, cell biology and therapy for alcoholism. These discoveries contribute to our understanding of alcoholic pathology in ways similar to the contributions of Ron Thurman. I know Ron Thurman would be pleased to celebrate the discoveries of Dr. Israel with the lectureship award."

The award presentation was followed by Israel presenting a heartfelt tribute to Ron Thurman's many accomplishments and the impact of his work on Israel's research and career. Israel presented his latest work entitled, 'Maternal, Genetic and Metabolic Influences on Ethanol Consumption in Rats.' This work demonstrates continuing breakthroughs on the genetic and environmental interactions that contribute to risk for alcoholism.

The Thurman award is given to distinguished researchers who contribute to our knowledge of alcohol and liver function and commemorates the life and scientific excellence of the late Ronald G. Thurman. For over thirty years, Thurman was an outstanding investigator in the fields of hepatic metabolism, alcoholic liver injury and toxicology and trained hundreds of scientists along the way. ■

The Bowles Center for Alcohol Studies

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

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