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FAS Researchers Honored at RSA Annual Meeting

Bowles Center for Alcohol Studies (CAS) researcher Kathleen K. Sulik, Ph.D., presented the T.K. Li Lectureship plenary address at the Research Society on Alcoholism (RSA) meeting in San Antonio, Texas, on June 27, 2010. Her talk, "Fetal Alcohol Spectrum Disorder: Research to Prevention," focused on her laboratory's imaging-based investigations of alcohol-induced birth defects, as well as the birth defects prevention-directed middle and high school curricula that she and her colleagues have developed.

Sulik is a professor in the UNC Department of Cell and Developmental Biology and the Bowles Center for Alcohol Studies. Her work aims to achieve a better understanding of the mechanisms, pathogenesis, and pathology associated with a variety of environmentally-induced and genetically-based birth defects. She hopes to use her findings to develop preventive measures relative to these defects.

T.K. Li, M.D., with Kathy Sulik, Ph.D.

The Lectureship that opens the RSA conference is named for T.K. Li, M.D., former director of the National Institute on Alcohol Abuse and Alcoholism, and honors his sustained commitment to excellence in alcohol research and its dissemination in practice and policy. It is a great honor to be selected to give this plenary lectureship. Dr. Sulik gave an inspiring presentation of her discoveries and fetal alcohol exposure prevention efforts.

CAS Postdoctoral Fellow Shonagh O'Leary-Moore, Ph.D., received both a Fetal Alcohol Spectrum Disorders Study Group (FASDSG) Merit Award and a Memorial Award from RSA at the June meetings.

The FASDSG Merit Award is presented to a graduate student, postdoc or fellow, who is a member of FASDSG, for outstanding research in the field of FASD. One Award is presented each year at the annual FASDSG meeting and includes a travel stipend. RSA Memorial Awardees are chosen among students or postdocs who have presented in RSA symposia. The award comes with a travel stipend, funded by donations to honor RSA members who have passed away within the past 5 years.

O'Leary-Moore came to the UNC Bowles Center for Alcohol Studies in 2007 for postdoctoral training in teratology under Kathy Sulik and continues to apply neuroimaging techniques, including diffusion tensor imaging (DTI), to the study of fetal alcohol exposure.

The CAS congratulates Drs. Sulik and O'Leary-Moore on these honors. ■

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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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A. Leslie Morrow, Ph.D., Editor-in-Chief; Elizabeth Thomas, 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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From Animal Models to Clinical Studies: Morrow Lab Elucidates the Therapeutic Potential of Neuroactive Steroids

It's the "where's the beef" question that most animal researchers have heard at least once after describing their findings to a new audience: "Yes, that's very interesting. But what do your findings mean for humans?" Establishing what scientists call the "translational relevance" of basic science research-that is, its implications for clinical practice-is sometimes challenging. Establishing the translational relevance of basic science research is particularly important in studies of alcohol and alcoholism, where the need for treatments is great and scientists and lay people alike look to animal research to provide clues to potentially useful therapeutic approaches.

Morrow Lab (left to right): Nikki Leonard, Alex Fetzer, Lihan Deng, Ana Maria Dumitru, Todd O'Buckley, Smita Gupta, A. Leslie Morrow, Ph.D., Chandler Walker, Jason Cook, and Patrizia Porcu, Ph.D.

Dr. A. Leslie Morrow, Professor of Psychiatry and Pharmacology and Associate Director of the Bowles Center for Alcohol Studies at UNC, has pioneered studies of an important class of neuromodulators known as neuroactive steroids in alcohol actions. She is also a pioneer in establishing the relevance of neuroactive steroids to the clinic. Produced by various glands and organs including the adrenals and brain, neuroactive steroids modulate the function of the brain's major inhibitory neurotransmitter, GABA. In experiments spanning more than a decade, the Morrow laboratory has demonstrated that neuroactive steroids are key contributors to alcohol sensitivity, which in humans predicts risk of alcoholism. Morrow and her colleagues demonstrated that administering moderate doses of alcohol in animal models increases concentrations of neuroactive steroids in both the bloodstream and the brain in an amount capable of altering GABAergic functioning. The lab also showed that acute administration of alcohol markedly increases concentrations of specific neuroactive steroids in the bloodstream and in brain areas important in mediating the cognitive and motor effects of alcohol. The increase in neuroactive steroid levels, which is caused by an increase in synthesis of neuroactive steroids by glands such as the adrenals, enhances GABAergic neurotransmission. Blocking the effect of alcohol on neuroactive steroid levels through manipulations such as adrenalectomy or administration of the neuroactive steroid synthesis inhibitor finasteride mitigates a range of alcohol effects, including its relaxing, antidepressant, sedating, and cognitive-impairing properties-findings suggesting that these alcohol effects are at least in part mediated by neuroactive steroids.

Neuroactive steroids can be synthesized by multiple glands and organs including the adrenals, brain, testes, and ovaries. Morrow demonstrated the particular importance of the adrenals in alcohol enhancement of neuroactive steroids in the bloodstream and the brain by showing that such enhancement does not occur in adrenalectomized animals. In some of their most recent animal work, published in 2010, Morrow's group established the molecular mechanisms that underlie alcohol enhancement of neuroactive steroid synthesis in the adrenals. They found that release of the adrenocorticotrophic hormone (ACTH) and *de novo* synthesis of a specific cholesterol transporter known as StAR in the adrenals are both required in order for alcohol to increase levels of neuroactive steroids. In an elegant series of experiments, they demonstrated that ethanol increases both ACTH release and StAR synthesis and that these effects are independent of one another. Further, both ACTH release and StAR

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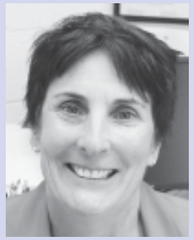

A. Leslie Morrow, Ph.D.

Affiliations

Associate Director, UNC Bowles Center for Alcohol Studies; John Andrews Distinguished Professor, Departments of Psychiatry and Pharmacology.

Recent Publications

Ethanol induction of steroidogenesis in rat adrenal and brain is dependent upon pituitary ACTH release and de novo adrenal StAR synthesis. Boyd KN, Kumar S, O'Buckley TK, Porcu P, **Morrow AL**. J Neurochem. 112(3):784-96 (2010).

Tolerance to ethanol-induced elevation of neuroactive steroids involves the loss of pituitary ACTH release and adrenal StAR phosphorylation. Boyd KN, Kumar S, O'Buckley TK, **Morrow AL**. J Neurochem. (In Press, 2010).

Naltrexone Selectively Elevates GABAergic Neuroactive Steroid Levels in Heavy Drinkers With the ASP40 Allele of the OPRM1 Gene: A Pilot Investigation. Ray LA, Hutchison KE, Ashenhurst JR, **Morrow AL**.. Alcohol Clin Exp Res. 1;34(8):1479-1487 (2010).

Differential effects of ethanol on serum GABAergic 3α,5α/3α,5β neuroactive steroids in mice, rats, cynomolgus monkeys, and humans. Porcu P, O'Buckley TK, Alward SE, Song SC, Grant KA, de Wit H, **Morrow AL**.. Alcohol Clin Exp Res. 1;34(3):432-42 (2010).

Pregnenolone and ganaxolone reduce operant ethanol self-administration in alcohol-preferring P rats. Beesheer, J, Lindsay TG, O'Buckley TK, Hodge CW, **Morrow AL**.. Alcohol Clin Exp Res. (In Press, 2010)

Website

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synthesis are necessary, but not sufficient, for the occurrence of alcohol-induced elevation of neuroactive steroids in the bloodstream and brain. ACTH is released by the pituitary gland to modulate adrenal gland functioning in response to stress and other stimuli. The results suggest that alcohol-associated increases in neuroactive steroids are caused by stimulation of the hypothalamic-pituitary-adrenal (HPA) axis, the body's main system for responding to stress.

Chronic exposure to alcohol results in tolerance to its ability to increase neuroactive steroid levels as well as to neuroactive steroid-mediated behavioral effects of alcohol such as relaxation and sedation. In another 2010 publication, Morrow and her colleagues pinpointed the mechanisms of tolerance to alcohol-induced increases in neuroactive steroids as the disruption of ACTH release and StAR phosphorylation. The lab has thus elucidated mechanisms for loss of alcohol-induced increases in neuroactive steroids, a phenomenon that might contribute to behavioral tolerance to alcohol and influence the progression to alcoholism.

"Neuroactive steroids are key contributors to alcohol sensitivity."

Considered in aggregate, the large body of evidence amassed by the Morrow lab through animal studies suggests that alcohol-induced elevation of neuroactive steroids is an important mediator of sensitivity to alcohol. The loss of alcohol-induced responsiveness of neuroactive steroids with chronic alcohol consumption might promote excessive alcohol intake to achieve alcohol's desired effects. Morrow is now using the evidentiary foundation from her animal research on the mechanisms and roles of neuroactive steroids to guide exciting translational work on neuroactive steroids in humans.

For example, Morrow and colleague Patrizia Porcu, Ph.D., also at UNC Bowles Center for Alcohol Studies, have paved the way for investigations of the potential role of neuroactive steroid responses as a biomarker for alcoholism risk. Consistent with the idea that loss of alcohol-induced responsiveness of neuroactive steroids with chronic alcohol consumption might promote excessive alcohol consumption to achieve alcohol's desired effects, Morrow postulates that blunted neuroactive steroid responses to physiological and/or pharmacological challenge might predict risk for alcohol abuse and alcoholism. In order to test this hypothesis, it is necessary to measure neuroactive steroids in humans. Until recently, the specific neuroactive steroids of interest could not be measured in humans with available methods. Porcu and Morrow developed a state-of-the-art method for efficient, specific, and sensitive measurement of the relevant neuroactive steroids in human serum. This method promises to have widespread utility in investigating the role of neuroactive steroids in human health and disease and in discovering biomarkers and developing therapeutic agents for alcoholism and other disorders.

The feasibility of using neuroactive steroid responses as biomarkers is illustrated by Morrow and UNC colleague Dr. Susan Girdler's recent findings in depression. In a study of 28 women, those in clinical remission from depression had lower concentrations of specific neuroactive steroids in their bloodstream both before and after being administered the steroid progesterone than did women without a history of depression. These results show that abnormalities in neuroactive steroid levels and responses can be indicators of a clinical condition and suggest that a history of clinical depression is associated with persistent neuroactive steroid deficits.

In another line of research, Morrow recently collaborated with UCLA investigators to shed light on the potential role of neuroactive steroids in the mechanism of action of naltrexone, a drug currently in clinical use for treatment of alcoholism. Naltrexone is effective in reducing alcohol craving and drinking and in mitigating the rewarding effects of alcohol, but the mechanisms by which naltrexone effects these changes have not been well characterized. Knowing that an irregularity in a gene known as OPRM1 is associated with enhanced therapeutic effects of naltrexone and that naltrexone disinhibits the HPA axis, Morrow postulated that

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The Director's Column

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

This Center Line presents a wonderful example of what all the Bowles Center for Alcohol Studies faculty want to do: make discoveries that improve health. Biology, physiology, biochemistry and the brain are incredibly complicated and only a few hard working dedicated scientists are able to make important basic science discoveries. Discoveries are hard to make. Even fewer can translate their basic discoveries to human clinical discoveries that in time are translated to improved health and medical care. This issue includes two Center for Alcohol Studies faculty who have done this. I admire their passion to make discoveries that improve human lives and feel blessed to have such wonderful faculty.

The discoveries of Leslie Morrow on neuroactive steroids are exciting, novel and are changing the world. Morrow's group has developed sensitive methods to measure them and recently discovered details on how they are synthesized and how they contribute to acute sensitivity to alcohol. The acute sensitivity to alcohol is known to be an important predictor of risk for alcohol dependence, e.g. a low sensitivity to alcohol increases risk of alcoholism. Leslie Morrow has shown genetic and environmental factors regulate neuroactive steroids. Almost all mental disorders are associated with alterations in the hypothalamic (brain) – pituitary – adrenal axis (brain-body hormone axis). However, scientists could not figure out if these hormonal changes are due to the stress of disease or actually contributing to the disease. Efforts to measure hormones as diagnostic factors also never worked. Morrow has discovered that neuroactive steroids, hormones never before carefully measured (or known), are key active agents. This breaks open

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naltrexone might selectively elevate neuroactive steroid concentrations in drinkers with the OPRM1 irregularity. Among 32 heavy drinkers, naltrexone compared with an inactive placebo increased neuroactive steroid concentrations in those with the OPRM1 irregularity but not among those without it. These results are consistent with a role of neuroactive steroids in the clinical efficacy of naltrexone.

Morrow believes that treatment with neuroactive steroids themselves might be therapeutic in alcoholism and could be helpful in alleviating symptoms of alcohol withdrawal. She is actively seeking collaborators to test potential therapeutic effects of neuroactive steroids and their precursors in human alcoholism. "Our animal research and now our research in humans have yielded numerous findings suggesting that neuroactive steroids could be useful in the treatment of alcoholism," says Morrow. "Neuroactive steroids increase alcohol sensitivity; they reduce heavy alcohol consumption in animal models of alcoholism; they reduce withdrawal symptoms; they mitigate neuroinflammation–I could go on and on. Converging lines of evidence suggest that the therapeutic potential is there. But we won't know whether neuroactive steroids are really helpful in alcoholism until we test them in human alcoholics. That's where we want to go next." Morrow points to the success of a proof-of-concept trial that showed the potential therapeutic utility of a neuroactive steroid for cognitive symptoms in schizophrenia, noting the presence of cognitive deficits in alcoholism as well. "Where's the beef? Here's the beef," says Morrow. "This is what it's all about: using our basic science findings to provide rational, evidence-based direction for interventions that help people." ■

the field and may at last explain how altered body hormones may induce mental dysfunction. Her discoveries are beginning to provide new ways to diagnose mental disease as well as treat mental disease.

Kathy Sulik has created exciting new ways to detect fetal alcohol brain toxicity using neuroimaging. She has advanced her basic studies of alcohol induced facial morphology that identifies fetal alcohol syndrome to a broader level by imaging the brain and following alcohol-induced dysmorphology in brain. This will allow better identification of babies with alcohol insults so we know who needs treatment. Prevention is even better. Sulik has taken her basic discoveries and translated them to education and prevention messages about how the brain develops and how alcohol damages the fetus. She has developed simple experiments that can be done in elementary level classes, and more complex experiments for middle and high schools. These experiments excite students who carry the message home to the family. "Do not drink if you are or might get pregnant, because alcohol hurts the baby."

The discoveries of Morrow and Sulik are improving health. I admire their success and am proud to have them in our Center for Alcohol Studies. ■

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