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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Thiele Laboratory Neuropeptide Research Reveals Therapeutic Targets for Alcoholism

Recent years have witnessed an explosion of research into the functions of neuropeptides—compounds that are composed of at least two amino acids linked by peptide bonds and that are found in neural tissue. Neuropeptides have been identified throughout the animal kingdom. Approximately 100 of them have been found in the mammalian brain. Neuropeptides appear to mediate a vast array of functions in both health and disease. Research suggests that neuropeptides are important modulators of phenomena as various as the foraging behavior of honeybees and the "runner's high" that sustains marathoners through long-distances. Neuropeptides have also been implicated as contributing to pathologic conditions including diabetes, obesity, Alzheimer's disease, and drug addiction.

Thiele Lab (Left to Right): Dayna Hayes, Todd Thiele, PhD, Angela Sparrow, Emily Lowery, Montserrat Navarro, PhD, Lorraine Ko, Ping He.

Dr. Todd Thiele, associate professor and director of research services in the department of psychology and member of the curriculum of neurobiology and the Bowles Center for Alcohol Studies at UNC, is particularly interested in how neuropeptides contribute to alcohol abuse and alcoholism. A quietly intense scientist, Thiele is known for his systematic and thorough approach to tackling tough scientific questions. In a multipronged program of studies, Thiele has elucidated the role of several neuropeptides in alcohol consumption and has identified potential biological targets for treatments for alcohol abuse. Thiele's work on alcohol and neuropeptides initially focused on neuropeptide Y, a signaling protein widely distributed throughout the brain. He found that mice genetically altered to be deficient in this neuropeptide drank much more alcohol than mice with normal neuropeptide Y levels (wild-type mice) and were more resistant to the sedative and hypnotic effects of alcohol. Conversely, mice genetically altered so that they overproduced neuropeptide Y drank less alcohol and were more sensitive to alcohol's sedative and hypnotic effects than mice with normal neuropeptide Y levels. Thiele's masterful demonstration of an inverse relationship between neuropeptide Y levels and alcohol consumption or resistance was published in the prestigious scientific journal *Nature*.

Thiele next turned to the question of how neuropeptide Y affects the brain to cause changes in alcohol consumption. Neuropeptide Y binds to several receptor subtypes found on brain cell surfaces to cause changes in cell function. In a series of studies with mice genetically altered to lack specific receptor subtypes, Thiele identified the receptor subtypes that appear to be responsible for neuropeptide Y effects on voluntary alcohol consumption. Mice lacking the Y1 receptor or the Y2 receptor, but not the Y5 receptor, showed altered alcohol consumption compared with wild-type mice.

Having shown that neuropeptide Y modulates voluntary alcohol consumption and having identified the receptors involved, Thiele next sought to address the specific brain regions important in mediating neuropeptide Y effects. Thiele and graduate student Dayna Hayes assessed neuropeptide Y amounts in the brains of two strains of mice: one that naturally drinks large amounts of alcohol and another that avoids alcohol. They found that the high-alcohol-drinking mice compared with the alcohol-avoiding mice had substantially reduced levels of neuropeptide Y in specific brain regions including the shell of the nucleus accumbens, the basolateral amygdala, and the central nucleus of the amygdala (Figure). These results are consistent with the possibility that low neuropeptide Y levels in these regions predispose the high-drinking mice to increased alcohol consumption. To further explore this possibility, Thiele administered substances (viral vectors)

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Affiliations

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Education and Training

PhD and MS in Psychology, Kansas State University, Manhattan, KS, 1995 and 1992; BS in Psychology, University of Wisconsin, Madison, WI, 1989.

Recent Publications

Sparta, DR, Fee, JR, Knapp, DJ, Breese, GR, **Thiele, TE.** Elevated anxiety-like behavior following ethanol exposure in mutant mice lacking neuropeptide Y (NPY). Drug Alcohol Depend. Published Online, 2007.

Fee, JR, Knapp, DJ, Sparta, DR, Breese, GR, Picker, MJ, **Thiele, TE**. Involvement of protein kinase A in ethanol-induced locomotor activity and sensitization. Neuroscience. 140(1): 21-31, 2006.

Hayes, DM, Knapp, DJ, Breese, GR, **Thiele, TE**. Comparison of basal NPY and CRF levels between the high ethanol drinking C57BL/6J and low ethanol drinking DBA/2J inbred mouse strains. Alcoholism: Clinical & Experimental Research, 29: 721-729.

Navarro, M, Cubero, I, Chen, AS, Chen, HY, Knapp, DJ, Breese, GR, Marsh, DJ, **Thiele TE**. Effects of melanocortin receptor activation and blockade on ethanol intake: a possible role for the melanocortin-4 receptor. Alcohol Clin Exp. Res. 29(6): 949-57, 2005.

Website

www.med.unc.edu/alcohol/thiele

that cause secretion of neuropeptide Y into specific brain regions and examined subsequent effects on alcohol consumption in mice. Administration of a viral vector causing neuropeptide Y secretion within the central nucleus of the amygdala in high-alcohol-drinking mice significantly reduced alcohol consumption relative to that in high-alcohol-drinking mice who were not administered the viral vector.

Thiele and his laboratory extended their studies of neuropeptide Y to assess its involvement in the alcohol withdrawal syndrome, which is manifested by neurologic symptoms such as difficulty concentrating, anxiety, and hallucinations and by motor symptoms ranging from muscle tremors to convulsions. The alcoholic's continued drinking is motivated in part by the need to prevent or alleviate these symptoms. Knowing that neuropeptide Y is involved in alcohol drinking as well as emotional responses, Thiele hypothesized that neuropeptide Y might mediate the anxiety that occurs during the alcohol withdrawal syndrome. With graduate students Dennis Sparta and Jon Free and fellow Bowles Center for Alcohol Studies scientists Drs. George Breese and Darin Knapp, Thiele found that mice deficient in neuropeptide Y compared with mice with normal levels of neuropeptide Y indeed show heightened withdrawal-associated anxiety as measured by established laboratory tests of emotionality. These data suggest that neuropeptide Y may modulate alcohol withdrawal-associated anxiety.

Thiele and his laboratory have also explored the role of another group of neuropeptides—the melanocortins—in alcohol consumption. With colleague Dr. Montserrat Navarro and others at the Bowles Center, Thiele explored the roles of specific cellular receptors (the melanocortin-3 and melanocortin-4 receptors) in alcohol consumption. In one experiment, high-alcohol-drinking mice were found to reduce their drinking after infusion of an agent that activates melanocortin-4 receptors and to increase their drinking after infusion of an agent that shuts down melanocortin-4 receptors. Considered in the context of other data, the results suggest that melanocortin receptor signaling modulates voluntary alcohol consumption and highlight the promise of compounds affecting melanocortin receptors for treating alcohol-abuse disorders.

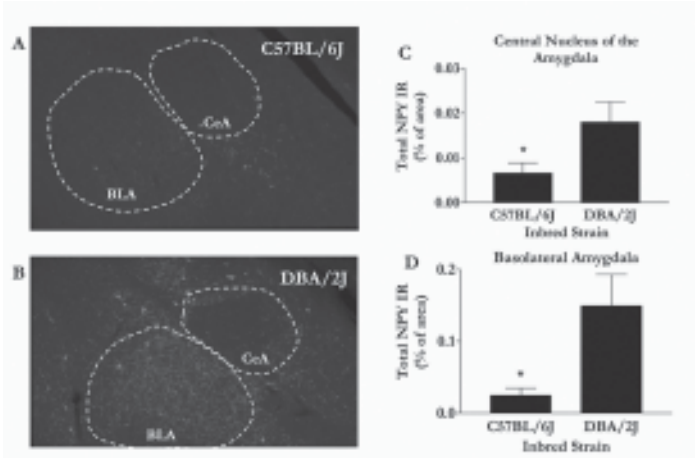

Figure: Neuropeptide Y immunofluorescence in the amygdala. Brain sections from high-alcohol-drinking mice (C57BL/6J) (Panel A) and alcohol-avoiding mice (DBA/2J) (Panel B). Panels C and D show quantification of immunofluorescence (reflecting levels of neuropeptide Y) in the central nucleus of the amygdala and the basolateral amygdala. From Hayes et al. Alcohol Clin Exp Res 2005;29:721-729.

Thiele and his colleagues have also provided evidence of therapeutic promise of compounds that affect corticotropin releasing factor, another neuropeptide that is widely distributed in the brain. They have recently found that treating high-alcohol-drinking mice with a drug that shuts off a specific corticotropin releasing factor receptor (the corticotropin releasing factor-1 receptor) prevents the surge in alcohol drinking that occurs after a period of alcohol deprivation in these animals. In another study, they showed that administration of a drug that shuts off the corticotropin releasing factor-1 receptor protected mice from the increase in alcohol drinking caused by stress.

When neuropeptides bind to receptors on brain cells, they initiate a cascade of events that alter cellular function and, ultimately, determine how these cells will

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The Director's Column

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

Peptide neurotransmitters are clearly at the core of addiction. For many years, we have known that opiate peptides play a role in regulating sensations of reward and good feelings. Now we know that anti-opiate drugs such as naltrexone, an opiate receptor antagonist, are useful in reducing craving for alcohol and helping maintain abstinence. There are many more peptides that are major factors in alcohol dependence. Peptides are key to regulating anxiety, mood, hunger and eating. They show great promise in improving our understanding of what goes wrong in addiction.

Many of the peptides involved in alcoholism originate in neurons in the hypothalamus, a key brain region that controls major hormone cycles as well as regulating feeding behavior. Neurons in the hypothalamus make peptides and send them across the brain via axonal projections. These peptides regulate initiation of eating and satiety, an important signal to stop consumption through processes that overlap with the drive to drink. Likely these drives are shifted to "hunger" for alcohol (craving) that is learned and then associated with environmental events like the evening, "I need a drink" response that many have after work.

One exciting opportunity in our field is to discover how altering peptide responses might help people reduce consumption or stop drinking. Currently there are no approved drugs that antagonize Neuropeptide Y (NPY) or corticotropin releasing factor (CRF), although there are ongoing clinical trials with some experimental compounds. In the absence of a portfolio of peptide antagonists, Todd Thiele has brilliantly used transgenic mice with modified peptide signaling to further establish the role of these peptides in alcohol drinking behavior. These studies require arduous breeding and other controls to avoid the traps of transgenic mice studies. Dr. Thiele has elegantly established that key peptides control drinking behavior. His studies are leading the field in understanding what peptides in brain are regulating drinking. NPY and CRF are among the most important.

We recently found decreased NPY in alcoholic human brain, consistent with increased drinking behavior in mice that have decreased NPY expression. These studies provide a foundation for pharmaceutical development of drugs that could test his hypotheses and maybe someday help the afflicted to stop drinking and regain control of their lives. With scientists like Todd Thiele, I know that further scientific progress will eventually bring these important findings to bear on the treatment of alcoholism. ■

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affect behavior. One of the key steps in this cascade of events is alteration of the activity of the intracellular enzyme *protein kinase A*. All of the neuropeptides that Thiele and his colleagues have shown to be important in alcohol effects—neuropeptide Y, melanocortins, and corticotropin releasing factor—impact protein kinase A activity. Possibly, the protein kinase A signaling pathway constitutes a shared substrate by which these neuropeptides affect alcohol consumption. In support of this possibility, Thiele found that mice genetically engineered to lack a structural component of protein kinase A (i.e , the regulatory II β subunit) drank significantly more alcohol than normal mice with functional regulatory II β subunits. In addition, mice lacking the regulatory II β subunit were less sensitive to the sedative effects of alcohol than normal mice but more sensitive to the locomotor stimulant effects of alcohol and to alcohol-induced locomotor sensitization (in which the locomotor response to alcohol is increased with repeated administration of alcohol). These results suggest that the regulatory II β subunit of protein kinase A contributes to regulation of alcohol intake and intoxication. In other research, Thiele and his colleagues provided evidence suggesting that, while the regulatory II β subunit is important in alcohol consumption, it is not a key mediator of pre-consummatory behavior directed at obtaining alcohol.

Thiele's productivity and systematic approach to posing and answering scientific questions have yielded tremendous benefits to the alcohol field. "Our work has provided a better understanding of how neuropeptides modulate alcohol ingestion," says Thiele. "The data point to important roles of several neuropeptides in alcohol drinking and reveal several potential targets for development of therapeutic approaches for alcohol abuse and relapse behaviors." ■

CONGRATULATIONS

Dr. Fulton T. Crews
Received the 28th Annual
RSA Distinguished Researcher Award
on July 7, 2007, in Chicago.

This is RSA's most prestigious award for scientific excellence.

Congratulations from CAS Faculty and Staff.

CAS Graduate Students Receive RSA Awards

Two graduate students working in the Bowles Center for Alcohol Studies (CAS) received awards for their outstanding research at the 30th Annual Research Society on Alcoholism (RSA) scientific meeting in Chicago.

Pharmacology graduate student Katie Kelm and neurobiology graduate student Tiffany Wills received the two most prestigious RSA awards given annually to pre-doctoral graduate students across the country. Kelm won the 2007 RSA Enoch Gordis Research Recognition Award, and Wills received the 1st Annual RSA Memorial Award.

Graduate Students Katie Kelm and Tiffany Wills

Kelm, working with Drs. Hugh Criswell and George Breese in the neuropharmacology section, won the Gordis Award for best student poster presentation at July's meeting. Her abstract entitled, "The role of inositol 1,4,5-triphosphate and ryanodine receptors in ethanol-enhanced GABA release," was selected following rigorous scientific, aesthetic and oral reviews by a committee of esteemed scientists. Kelm's primary paper on this work has been accepted for publication in the Journal of Pharmacology and Experimental Therapeutics.

Wills, working with Drs. Darin Knapp, David Overstreet and George Breese in neuropharmacology, won the RSA Memorial Award for her symposium presentation, "Are adolescent rats more sensitive to the effects of multiple withdrawals from ethanol?" This new award is presented to one pre- and one post-doc student each year and is awarded in honor of eminent RSA members who have recently passed away. Wills has a manuscript in preparation for this work that will be submitted in August.

This year's RSA meeting had over 1500 attendees. UNC CAS graduate students and faculty presented their research in 10 symposia and 34 posters during the five-day event. The RSA provides a forum for communication among researchers who share common interests in alcoholism. The Society's purpose is to promote research that can lead the way toward prevention and treatment of alcoholism. ■

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.

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