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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Alcoholism and Obesity: Overlapping Brain Pathways?

Thiele Research Team: Jon Fee, Dr. Todd Thiele, Dennis Sparta, Alex Mason

Name the condition characterized by the following features:

- Involves excessive consumption of caloric substances
- Involves addictive behavior
- Is harmful to health and, in many cases, fatal
- Affects millions of Americans
- Was once thought to be a failure of willpower
- Has been termed a "lifestyle" illness
- Is now conceptualized as a disease linked to both environmental and genetic causes

"That's easy," you may say. If you said "Obesity," you would be correct. However, if you said "Alcoholism," you would also be correct. Both obesity and alcoholism are prevalent and preventable causes of death that result from excessive consumption of caloric substances. Like obesity, alcoholism was once ascribed to a weak will but is now understood to be environmentally and biologically determined. Todd Thiele, who is an Assistant Professor in the University of North Carolina's Department of Psychology and the Bowles Center for Alcohol Studies, heads research efforts devoted to exploring the physiologic basis of the striking parallels between obesity and alcoholism. Thiele hypothesizes that some of the brain signaling proteins that mediate excessive eating and weight gain also mediate uncontrolled alcohol drinking. By understanding the physiologic commonalities between excessive alcohol drinking and excessive eating, Thiele hopes to shed light on intervention strategies, such as pharmaceutical compounds, that can help those who suffer from obesity and/or alcoholism. "We are particularly interested in identifying physiologic substrates that underlie food intake and body weight as well as alcohol intake," says Thiele. "The idea is that alcohol is a caloric compound, and alcohol intake and food intake are both reinforcing consummatory behaviors. It is therefore possible that overlapping pathways are involved in uncontrolled eating and excessive ethanol drinking."

Thiele and his laboratory have recently explored the role of a group of signaling proteins, the *melanocortins*, in alcohol consumption. Melanocortin agonists are known to inhibit food intake and cause significant reduction of body weight in animal models. Are the melanocortins also involved in alcohol consumption? Thiele approached this question by infusing the drug MTII, which mimics the effects of melanocortins at specific cellular receptors (the melanocortin-3 and melanocortin-4 receptors), into the brains of mice that habitually drink large amounts of alcohol. MTII reduced both voluntary alcohol drinking and food intake in these animals. Pretreatment of mice with a drug that blocks melanocortin-3 and -4 receptors prevented the MTII-associated reduction of alcohol drinking. These findings support a key role of melanocortins in alcohol intake and suggest that the effects of melanocortins on alcohol intake are mediated by the actions of melanocortins at the melanocortin-3 and -4 receptors. These results are also consistent with Thiele's hypothesis of a shared physiologic substrate of alcohol intake and food intake. Next, Thiele and his colleagues will extend this series of experiments by examining alcohol and food intake in mice bred to lack the melanocortin-3 receptor.

Much of Thiele's recent work focuses on a signaling protein known as *neuropeptide Y*. Previous research suggests that neuropeptide Y, which is

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Todd E. Thiele, Ph.D.

Birth: 13 Jan 1967

Education: Ph.D. in Psychology, Kansas State University, 1995; M.S. in Psychology, Kansas State University, 1992; B.S. in Psychology, University of Wisconsin-Madison, 1989.

Experience: Assistant Professor, Dept. of Psychology and the Bowles Center for Alcohol Studies, UNC-CH (2001 to present); Research Scientist, Alcohol and Drug Abuse Institute, Univ. of Washington (1998 to 2001); Postdoctoral Research Fellow, supported by the NIAAA. Mentor: Dr. Ilene Bernstein, Univ. of Washington (1995 to 1998); Predoctoral Research Fellow, supported by the NIAAA. Mentors: Drs. Stephen W. Kiefer and Jerome Frieman, Kansas State Univ. (1995).

Honors and Awards: Junior Faculty Development Award from the UNC-CH (2001 to present); Mason and Linda Stephenson Faculty Award, Psychology Dept., UNC-CH (2001 to present); Junior Investigator Awards, Research Society on Alcoholism (award supported by NIAAA; 1997, 1998); Merit Award, Research Society on Alcoholism (award supported by NIAAA and RSA; 1995).

Web page: http://www.med.unc.edu/alcohol/faculty/Thiele/Thiele.htm

Research funded by NIAAA.

found throughout the brain, is a key mediator of functions ranging from food intake to emotional responses. For example, in animal models, infusion of neuropeptide Y into the brain dramatically increases food intake. Other experiments show that infusions of neuropeptide Y can alleviate anxiety in animal models. Thiele has found that neuropeptide Y also appears to be an important regulator of alcohol intake. Neuropeptide Y becomes physiologically active by attaching to one of several receptor subtypes found on brain cell surfaces. Thiele found that mice lacking one of these receptor subtypes—the Y1 receptor—drank significantly more alcohol than normal mice (Figure 1). Given the diverse role of NPY, it will be important to determine how Y1 receptors modulate alcohol consumption, which may include NPY pathways involved with feeding, integration of emotional behavior, and/or other neurobiological functions.

"Common mechanisms may be involved in uncontrolled eating and excessive ethanol drinking."

Thiele and his laboratory, including graduate students Jon Fee and Dennis Sparta and laboratory technician Alex Mason, have recently extended this investigation of neuropeptide Y to assess its involvement in the alcohol withdrawal syndrome, which occurs when alcohol is withheld from an animal or human addicted to it. The alcohol withdrawal syndrome, which can be life-threatening, is manifested by neurologic symptoms such as difficulty concentrating, anxiety, and hallucinations and by motor symptoms ranging from muscle tremors to convulsions. For the alcoholic, prevention or alleviation of these symptoms constitutes a powerful motivator to continue drinking. Thiele, knowing that neuropeptide Y is involved in alcohol drinking as well as emotional responses such as anxiety, wondered whether neuropeptide Y might mediate the anxiety that occurs during the alcohol withdrawal syndrome. Working with Bowles Center collaborators Drs. George Breese, Darin Knapp, and David Overstreet, Thiele found that mice deficient in neuropeptide Y (because they lack a gene necessary to produce the neuropeptide) 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.

When signaling proteins such as neuropeptide Y and the melanocortins attach to receptors on brain cells, they initiate a cascade of events that alter cellular function and, ultimately, determine

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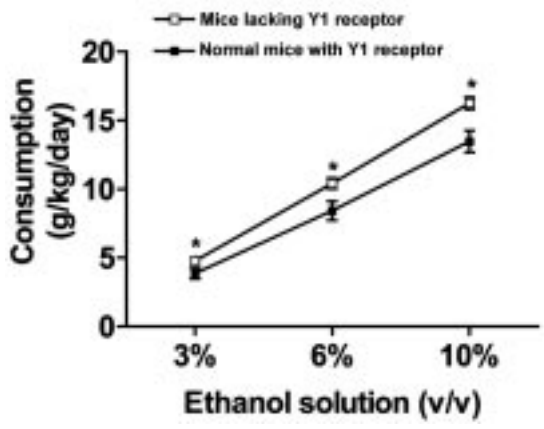

Figure 1. Mice lacking the Y1 receptor consume significantly (*p<0.05) more alcohol than do normal mice with intact Y1 receptors. All values are means ± standard errors.

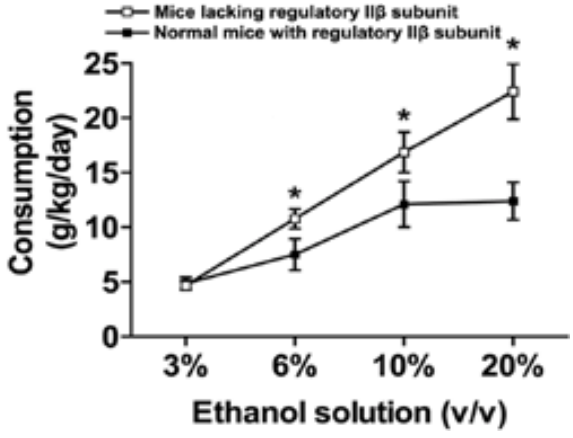

Figure 2. Mice lacking the regulatory IIb subunit of protein kinase A consume significantly (*p<0.05) more alcohol than do normal mice with intact regulatory IIb subunits. All values are means ± standard errors.

The Director's Column

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

Both alcoholism and obesity have genetic and behavioral components. Genetics plays an important role in determining health. Factors such as behavior also play a role in health, and we have learned that a lot of behavior is inherited. Genomics provides opportunities to explore the relationship between genes and health. Behavioral studies in mice are just beginning to provide an understanding of how genes interact with the environment to regulate behavior. In mouse studies, obesity is fairly easy to investigate because mice can eat as much as they want and it is easy to spot obesity in mice. Scientists have found genes that can cause obesity. Could these genes also play a role in alcohol drinking behavior?

Alcohol consumption is a fairly simple behavior to measure. If mice or rats or monkeys or higher primates are given a choice of water or alcohol (2-10% alcohol in water - similar to the concentration of alcohol in beer) various genetically different strains have markedly different preferences for alcohol compared to water. Some strains prefer to drink from the water tube 80-90% of the time whereas others prefer to drink from the alcohol tube 80-90% of the time. Certain rat strains have been bred to have a high alcohol preference, creating genetic models for alcoholism. The use of transgenic mice that have modifications in specific genes allow scientists to determine how genetic modification alters behaviors. This is an exciting approach to understanding the fundamentals of gene-environment-behavior interactions. Certain fundamental genes may have such pronounced effects on behaviors like consumption (alcohol or food) that they are easily measured in mice in a controlled environment.

Human behavior is much more complex and in theory we are capable of consciously regulating our behavior to healthy behaviors. Education helps; however, responses to stress, trauma and other major environmental factors can cause reactive behavior not chosen for health benefit. Addiction involves loss of control over behavior, in spite of the harm it causes. Understanding the key genes regulating alcohol consummatory behavior will lead us to key genomic mechanisms that will help unlock the mystery of addiction and complex behavior. This knowledge will lead to new ways to help people live healthier lives. Go Todd.

Our clinical efforts are directed at helping people change their unhealthy addictive behaviors. Changing behavior is difficult, particularly when there are strong genetic factors contributing to the behavior. It is important that those of us in the field recognize that changing behavior in addiction treatment is equally effective as treatments attempting to change eating behavior. It is just as difficult to get hypertensive and diabetic patients to diet and exercise as it is to get addicted people to stop taking drugs. It is difficult, but it can be done. As we understand the fundamentals that drive the genetic determinants of behavior, we should be better able to help people live healthier lives.

Post-Doctoral Fellowships Now Available!

Our Center is offering post-doctoral fellowships in a multidisciplinary training program funded by NIAAA. Research is focused on molecular and cellular studies on alcohol actions. Applicants must have an M.D. or Ph.D., U.S. citizenship or permanent residency, and an interest in alcohol research. For more Information, visit www.med.unc.edu/alcohol/postdoc.htm.

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how these cells will affect behavior. One of the key steps in this cascade of events is alteration of the activity of an intracellular enzyme called *protein kinase A*. Alterations in protein kinase A activity depend on the activity of proteins such as neuropeptide Y and the melanocortins, which Thiele showed are important in alcohol consumption. Therefore, it is possible that the protein kinase A signaling pathway constitutes a shared substrate by which any of several proteins affect consumption of alcohol. In support of this possibility, Thiele found that mutant mice bred to lack a structural component of protein kinase A (i.e., the regulatory IIß subunit) drank significantly more alcohol than normal mice (Figure 2). The increased consumption in the mutant mice was specific to alcohol as these mice showed normal consumption of sweet solutions containing sucrose or bitter solutions containing quinine. Those mutant mice were also less sensitive to the sedative effects of alcohol than normal mice and had high levels of baseline anxiety. Thiele suggests that the heightened anxiety in these mice may contribute to their excessive alcohol consumption, which alleviates anxiety.

Thiele speaks enthusiastically about the implications of this research: "Every day, we are learning more about how eating and drinking are inextricably linked at the physiologic level. These physiologic commonalities help to explain why the behaviors of excessive food intake and excessive alcohol consumption share so many similarities. Together, our data suggest that compounds directed at neuropeptide Y and/or melanocortin receptors, both of which modulate the activity of protein kinase A, may be promising candidates for treating alcohol abuse and alcoholism as well as obesity. Several compounds affecting these signaling proteins are already in development for obesity. Our research suggests that they should also be explored for alcoholism."

Alcohol & Substance Abuse Program Helps People Conquer Addictions

ASAP Leaders: William Renn, Kathy Grace, Karen Ogden, James C. Garbutt, MD

The diseases of alcoholism and drug dependence severely strain our society, economy and health care system. For example, untreated addiction results in higher health care costs than heart disease, cancer and diabetes. Alcohol and drug addiction also harms family life and jeopardizes the safety of citizens. Individuals addicted to alcohol and drugs are often unable to stop abusing, regardless of devastating consequences. They need help to overcome their disease. Fortunately, help is available in the form of treatment programs.

The UNC Health Care's Alcohol and Substance Abuse Program (ASAP), established in 1998 and an affiliate of the Center, is a highly successful intensive-outpatient treatment program. The ASAP program, directed by William Renn, allows individuals to remain in their jobs, live at home, and receive the treatment they need to return to full social and psychological functioning.

"We treat the *people* who use the substances, and not the drugs they use . We individualize treatment," says Mr. Renn. ASAP treats alcohol and substance abuse addiction through programs utilizing cognitive behavior, motivational enhancement, and twelve-step therapies. Each individual's program is designed to allow them to continue to work, attend school, and participate in social relationships while dealing with their addiction. ASAP leaders and addiction therapists believe that this form of treatment is important to the success of one's recovery.

Most of the treatment is done in group therapy with the assistance of highly trained and committed addiction therapists. Each individual receiving treatment may attend two-hour sessions, up to four times per week. The first hour focuses on education about addiction and the second hour opens a forum for discussion about personal experience related to the education. Individual therapy and family therapy compliments the treatment groups. Some patients receive medications that prevent craving and facilitate recovery. ASAP's therapists also collaborate with Center researchers, physicians, and community organizations to advance the diagnosis and treatment of substance abuse disorders.

For more information about ASAP, visit www.med.unc.edu/alcohol/asap/welcome.htm or call (919) 402-1644.

The Bowles Center for Alcohol Studies

Tel. (919) 966-5678
Fax. (919) 966-5679

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

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A. Leslie Morrow, Editor-in-Chief; Angela D. Farrior, Managing Editor; Jane Saiers, Science Writer

UNC Bowles Center for Alcohol Studies
CB# 7178, Thurston-Bowles Building
University of North Carolina at Chapel Hill
Chapel Hill, North Carolina 27599-7178

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