

“The Developing Brain” at Morehead Science Center Explains the Dangers of Fetal Alcohol Exposure

The Center for Alcohol Studies (CAS) and the Morehead Planetarium and Science Center at UNC have worked together to develop a Science 360 module, “The Developing Brain,” that teaches the effects of fetal alcohol exposure. The 30-minute shows are presented each weekend during the spring and the fall and are open to the public.

CAS Professor Kathy Sulik provided the scientific content for “The Developing Brain,” an interactive show focusing on human brain development and the effects of alcohol on the brain as it forms. The show begins with a split-screen illustration of a normal child versus a child with fetal alcohol syndrome (FAS) whose features tend to be smaller and less developed. The audience is then shown a model of a normal brain compared with an FAS brain and the clear differences in the development of the important parts of the brain that affect cognition; reasoning, learning and comprehension are identified.

For the presentation, the audience is provided with i-clickers,

tools that allow viewers to answer multiple choice questions throughout the presentation that correspond to the information in the program, with the audience results displayed on screen. This approach allows a fun and interactive learning experience as audience members learn about the effects of alcohol on a developing embryo and fetus.

In “The Developing Brain,” audiences learn the amount of time it takes the brain to start developing in utero and how large an embryo is in its third week, when it is already vulnerable to alcohol-mediated damage. Audiences also learn that researchers use animal models to study the effects of alcohol on the brain, as animals, such as mice and fish, have brains that develop in similar ways to humans.

“What audiences should take away from this presentation is that the brain begins to develop very early in pregnancy, and alcohol can affect its development beginning at these very early stages until birth,” said Sulik. “This program is designed for everyone, but we really hope it will provide youth awareness about the effects of alcohol and subsequently aid in FAS prevention.”

A team of educators, including scientists, writers, producers, and designers, create each Science 360 program. Each module is presented by trained Morehead specialists; typically UNC graduate students in varying fields. “The Developing Brain” is supported by a grant from the National Institute on Alcohol Abuse and Alcoholism and will run through the end of the year. Two additional learning modules on alcohol, directed at elementary, middle, and high school students, are in the planning stages for next year.

For more information on this and other Science 360 programs, please visit <http://www.moreheadplanetarium.org>. ■



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Center Line, Vol. 20, No. 2 Published quarterly to bring readers a greater understanding of alcoholism research and the Center's mission.
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This document is supported by subscriptions and donations to the Bowles Center for Alcohol Studies; All research partially funded by NIAAA.

Breese Laboratory Elucidates Mechanisms of Stress in Alcohol Relapse

It's been fourteen months since I walked into my first Alcoholics Anonymous meeting. It's about thirteen months since I admitted that I am an alcoholic and I am powerless over alcohol. It's about twelve months since I started working the Twelve Steps. [Then] why did I buy the bottle of Margaritas and drink it on December 21st? . . . As soon as the bottle touched my lips I hated myself. How could I be doing this to myself again after all I'd been through in the past year? I wanted to throw the bottle through the window and get far away from it but I knew I would hug it near me until it was empty.

From "An Alcoholic Relapses" by Vicky S.

In alcoholism, the frequent occurrence of

relapses such as the one Vicky S describes is the norm rather than the exception. Many alcoholics try to stop drinking and fail. Half to two thirds of alcoholics who attempt abstinence relapse within months of initiating treatment. Even alcoholics who have been abstinent for years are prone to relapses. Most alcoholics relapse several times before achieving complete recovery. Alcoholic relapses can devastate alcoholics and their families, cause or perpetuate serious health problems, and result in lost jobs. Although relapses often seem sudden and unpredictable, with causes inscrutable even to the alcoholic,

scientific research suggests that relapse is provoked by specific, identifiable factors. Identification of these factors could help to pave the way for developing interventions that can decrease the probability of relapse. Dr. George Breese, Professor of Psychiatry and Pharmacology at the Bowles Center for Alcohol Studies, is at the forefront of efforts to elucidate the causes of relapse and to discover means of preventing it. A productive and

subsequent stimulation. This sensitization is reflected in the finding that behaviors or emotional responses mediated by these brain circuits are more easily elicited. Breese found that moderate alcohol drinking was followed by a mild negative affect (anxiety-like reductions in social interaction) during alcohol abstinence that could be sensitized (kindled) by exposing rats to three 5-day regimens of alcohol-containing diet with two days of



Breese Lab (left to right): Kui-Ling Huang, Man Huang, M.D., Ph.D., Tiffany Wills, Ph.D., Zhen Ming, M.D., Marc Weinberg, Ph.D., Sarah Sinnett, Buddy Whitman, M.S., Darin Knapp, Ph.D., Katie Kelm, Ph.D., Thomas McCown, Ph.D., Bonita Blake, DVM, Ph.D., Hugh Criswell, Ph.D., George Breese, Ph.D., David Overstreet, Ph.D., and Bob Angel, M.S.

respected leader in alcohol research with approximately 400 publications to his name, Breese uses animal models to study mechanisms and manifestations of alcohol withdrawal and relapse.

Breese and his colleagues are particularly interested in the emotional factors that can lead to craving and relapse. Working with Drs. Darin Knapp and David Overstreet, Breese established several years ago that multiple withdrawals from moderate alcohol exposure causes kindling of negative affect (anxiety and dysphoria). In kindling, repeated stimulation sensitizes brain circuits such that they are more easily activated in response to

abstinence between e a c h regimen. The Breese laboratory measures negative affect in rats with the social interaction

test, which quantifies the level of social behavior between pairs of rats. Rats are normally very social animals; decreases in social interaction behavior among rat pairs in the social interaction test is interpreted as reflecting the presence of anxiety and negative affect. Rats exposed to repeated withdrawals showed more negative affect in the social interaction test than rats exposed to the same concentration of alcohol given continuously over 15 days with only one period of abstinence at the end of alcohol exposure. After the negative affect associated with repeated withdrawals had abated, re-exposure to a single 5-day treatment and withdrawal

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George Breese, Ph.D.

Affiliations

Distinguished Professor, Psychiatry and Pharmacology; Head, Neuropharmacology Laboratory, Bowles Center for Alcohol Studies; Member, Neuroscience Center, University of North Carolina at Chapel Hill School of Medicine

Education and Training

Ph.D., Pharmacology, University of Tennessee, Memphis, 1965; M.S., Pharmacology, 1961, and B.S., Pharmacy, 1959, Butler University, Indianapolis; Postdoctoral Fellow in Pharmacology at NIMH, National Institutes of Health, Bethesda, MD, 1966-68.

Awards

John R. Andrews Professor, 2008 ASPET Award for Experimental Therapeutics, 2001.

Publications

Breese, G.R., Knapp, D.J., Overstreet, D.H., Navarro M, Wills TA, Angel RA. Repeated lipopolysaccharide (LPS) or cytokine treatments sensitize ethanol withdrawal-induced anxiety-like behavior. *Neuropsychopharmacology*, 33:867-876, 2008.

Breese, G.R., Overstreet, D.H., Knapp, D.J. Prior multiple ethanol withdrawals enhance stress-induced anxiety-like behavior during extended abstinence: Inhibition by CRF-1 and benzodiazepine receptor antagonists and by a 5-HT 1A-receptor agonist. *Neuropsychopharmacology*, 30:1662-1669, 2005.

Breese, G.R., Overstreet, D.H., Knapp, D.J. Conceptual framework for the etiology of alcoholism—a “kindling”/stress hypothesis. *Psychopharmacology*, 178:367-380, 2005.

Website

www.med.unc.edu/alcohol/breese

a week later resulted in the same degree of negative affect as measured after repeated withdrawals. The latter finding shows persistence of the repeated-withdrawal effect and is consistent with the presence of adaptive changes in brain circuitry.

Recently, Breese's group has been evaluating the effects of stress in their alcohol model. Breese hypothesizes that alcoholics' unique response to stressors is an important factor in relapse. He notes that, in human laboratory studies, exposure of alcoholics to stressful environmental or situational cues associated with alcohol elicits negative affect with reactions such as fear, sadness, anxiety, and anger. In the alcoholic, these affective responses are associated with craving for alcohol, one of the primary triggers of relapse. Unlike alcoholics, most healthy individuals do not have these negative affective responses when exposed to the same alcohol-related environmental or situational cues. Breese holds that the affective susceptibility of alcoholics to stressful environmental cues during abstinence—a primary basis for alcoholics to return to abusive drinking—reflects a persistent change in brain circuitry caused by alcohol abuse over time. Consistent with this possibility, Breese and his colleagues found that stress could substitute for the first two cycles of alcohol to sensitize withdrawal-induced negative affect. That is, repeated stresses followed by 5 days of alcohol exposure induced negative affect (as indexed by a reduction in social interaction) during withdrawal, but exposure to the repeated stresses in the absence of alcohol exposure did not induce negative affect. What's more, they found that stress exposure after repeated alcohol withdrawals sensitized stress-induced negative affect 3 days after alcohol withdrawal. This effect was not observed without previous alcohol exposure. Like the alcohol cycles, stress appears to have caused a persistent change in brain circuitry that led to increased susceptibility to withdrawal-induced negative affect, which in the alcoholic can stimulate craving and trigger relapse. The interchangeability of stress and a withdrawal episode could help to explain why abstinent alcoholics often relapse to drinking when they are stressed.

Breese and his coworkers next investigated the mechanism of the effect of stress in the repeated withdrawal model. They first

targeted corticotropin releasing factor (CRF). CRF, which occurs naturally in the body, is a peptide long known to be involved in stress responses. Breese reasoned that, if CRF is involved in mediating stress sensitization of negative affect, then administration of CRF should mimic the effect of stress in their repeated withdrawal model. In fact, when repeated CRF was substituted for stress prior to 5 days of alcohol exposure, this CRF/withdrawal protocol sensitized negative affect during alcohol withdrawal. That is, repeated administration of CRF followed by 5 days of alcohol exposure reduced social interaction behavior during withdrawal, but repeated administration of CRF in the absence of alcohol exposure did not affect social interaction behavior.

In an elegant set of experiments, Breese and his colleagues also demonstrated that a CRF antagonist—a drug that blocks the typical actions of the body's CRF—prevented sensitization of withdrawal-induced negative affect when it was administered during the sensitization process. Remarkably, the CRF antagonist significantly reduced negative affect after the third withdrawal even though it was administered only during the first two withdrawals or during the first two repeated stresses that substituted for the withdrawals. These findings demonstrate that pharmacological reduction of negative affect during early withdrawals or early exposure to stresses can mitigate the worsening of withdrawal-associated negative affect that occurs over repeated cycles of intoxication and withdrawal. That CRF sensitized negative affect in the withdrawal paradigm while CRF antagonists prevented this sensitization provides strong evidence for involvement of CRF in kindling of negative affect during alcohol withdrawal.

Breese and his colleagues next studied cytokines in their model. Cytokines are signaling molecules that, like CRF, have been demonstrated to be important in stress responses. Breese and his colleagues found that the restraint stress that they used in their stress/withdrawal protocol increased cytokines in rat brain. When repeated cytokines (MCP-1, TNF α , IL-1 β) were substituted for stress before alcohol exposure, this cytokine/withdrawal protocol (like the CRF/withdrawal protocol)

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The Director's Column

Fulton T. Crews, Ph.D.
Director,
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This issue of the Center Line reflects the broad spectrum of health effects of alcohol. Our Center's faculty cover areas including fetal development, medical screening for heavy drinking and appropriate interventions, and biological mechanisms of anxiety and mood that can change how individuals interact. Each of these is complex. A positive attitude and happiness are among the most important aspects of health. If moderate alcohol consumption triggers brain adaptation increasing anxiety and negative mood, this could promote heavier drinking contributing to progressive increases in drinking, a key element of progressing to dependence. Subtle changes over time are difficult or impossible to track in humans who have widely varied moods, experiences, genetics and environments that regulate these states. In animals, these are all controlled. Subtle persistent changes in mood due to repeated withdrawals from drinking, drinking and stress, as well as drinking and inflammation stress could markedly alter the life course. These factors increase anxiety and negative mood that may promote relapse.

Understanding the mechanisms of anxiety and persistent changes in mood will help many who suffer from anxiety in alcohol dependence and many other brain pathologies associated with anxiety. It is not clear if fetal exposure alters the subsequent mood of offspring, but it is clear alcohol can harm the fetus and prevention can stop it. Science 360 is directed at school children, but physician education of patients is also important. Our center uses all approaches, basic mechanisms of brain adaptation coupled with prevention messages for youth and adults. Hopefully, one or all will improve health. ■

CONGRATULATIONS to Dr. Robert Gwyther on Receiving the UNC Medical Alumni Association Distinguished Faculty Award

Gwyther received this year's award in recognition of his outstanding contributions as a physician, educator and champion of improved care for patients with substance abuse problems.

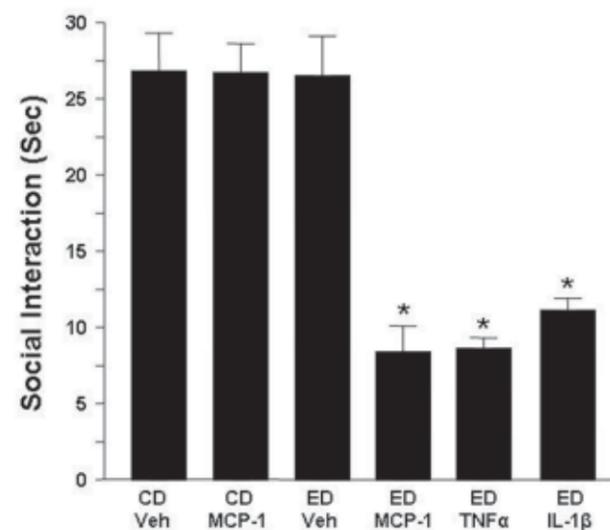


Figure: Repeated MCP-1 administration (100 ng/5 ml, i.c.v.) sensitizes ethanol withdrawal-induced anxiety. Rats were injected twice at weekly intervals with either vehicle or MCP-1 (or the cytokines IL-1 β or TNF α) while drinking control liquid diet (CD) and then were either continued on CD or switched to a 4.5% ethanol liquid diet (ED) for 5 days. MCP-1 was also given twice in a group exposed only to CD to test for an effect on social interaction in the absence of the ethanol exposure. MCP-1 (monocyte chemo-attractant protein-1); IL-1 β (interleukin-1 beta); TNF α (tumor necrosis factor-alpha); Veh (vehicle: artificial cerebrospinal fluid). *p<0.001 compared to CD-Veh or ED-Veh groups. Adapted from Breese et al. (2008) *Neuropsychopharm* 33:867.

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sensitized negative affect during alcohol withdrawal (see Figure). Considered in aggregate, these findings are consistent with the possibility that cytokines and CRF activated by stress contribute to stress-induced negative affect during alcohol withdrawal.

“One of the most important factors in alcoholism and alcohol research is the role of stress as a precipitant of craving and relapse,” says Breese. “Stress may contribute to relapse through a kindling-like process whereby it sensitizes negative affect. The increase in negative affect may promote heavy drinking and contribute to the progression to alcoholism. But we can't stop there. It is critical for us to understand exactly how stress interacts with chronic alcohol exposure to sensitize negative affect. Our studies show that stress causes release of cytokines and CRF in brain and that cytokines and CRF can substitute for stress to sensitize negative affect in our model. We are now beginning to look at particular brain areas where cytokines and CRF act on specific receptors to produce sensitization of alcohol-withdrawal-induced negative affect. We will be using multiple approaches, including behavioral, biochemical, and electrophysiological studies, to tackle this problem. If we can understand the specific mechanisms by which stress leads to craving and relapse, we can begin to target anti-relapse interventions to help Vicky S and millions of alcoholics like her in their quest to remain abstinent and healthy.” ■