



George Breese, Ph.D.

Affiliations

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

Distinguished Alumni Award from Butler University, 2005
ASPET Award for Experimental Therapeutics, 2001.

Recent Publications

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.

Criswell, HE, Breese, GR. A conceptualization of integrated actions of ethanol contributing to its GABA_{mimetic} profile: A commentary. *Neuropsychopharmacology*, 30:1407-1425. 2005.

Overstreet, D.H., Knapp, D.J., Angel, R.A., Breese, G.R. Reduction in repeated ethanol withdrawal-induced anxiety-like behavior by site-selective injections of 5-HT_{1A} and 5-HT_{2C} ligands. *Psychopharmacology*, 2006. In Press.

Website

<http://www.med.unc.edu/alcohol/faculty/BreeseGR/Breese.htm>.

one 5-day regimen of diet or 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. This kindling-like effect—in which repeated withdrawal episodes were associated with more severe withdrawal-associated negative affect than was a single withdrawal—occurred after relatively few courses of alcohol exposure. This finding suggests that kindling of affective responses can begin early during the course of alcoholism.

Breese and his colleagues went on to demonstrate that the impact of repeated withdrawals on negative affect is persistent and cumulative—defining characteristics of kindled phenomena. Persistence was demonstrated by the finding that, after the negative affect associated with repeated withdrawals had abated, re-exposure to a single 5-day treatment and withdrawal a week later resulted in the same degree of negative affect as measured after repeated withdrawals. Cumulative sensitization of negative affect was demonstrated by the finding that certain drugs administered only during the first two withdrawals reduced negative affect measured after the third withdrawal.

Negative affect associated with repeated withdrawals was mitigated by drugs that influence specific brain systems. For example, drugs that stimulate the 5HT_{2C} receptor substituted for withdrawal whereas drugs that block this receptor prevented the negative emotional effects of repeated withdrawals. These data suggest the possibility that prophylactic administration of 5HT_{2C} receptor antagonists could help counteract the progressively worsening negative affect observed during periods of abstinence. Based in part on results in Breese and colleagues' repeated-withdrawal paradigm, clinical trials have been initiated to explore effects of certain drugs in human alcoholics.

Drawing on research demonstrating the importance of stress in alcoholic relapse, Breese and his colleagues next investigated the impact of stress in the repeated-withdrawal paradigm. They found that stress could substitute for initial cycles of withdrawal to sensitize withdrawal-induced negative affect. This

interchangeability of stress and a withdrawal episode could help to explain why abstinent alcoholics often relapse to drinking when they are stressed. “To the abstinent alcoholic, stress might in some ways mimic the state of withdrawal,” says Breese. “The abstinent alcoholic may therefore respond to stress in the same way that he or she responds to negative affect as a withdrawal symptom—by drinking alcohol.”

On the basis of their findings, Breese and his colleagues propose that kindling provides a conceptual framework for understanding the etiology of alcoholism (See Figure Next Page). According to their model, withdrawals from repeated cycles of alcohol abuse engage the process of kindling early in the development of alcoholism. Kindling is associated with persistent neural changes (adaptation) that underlie the progression of alcohol use from occasional drinking to alcohol dependence. Cumulative adaptive neural changes caused by repeated withdrawals might (1) stimulate craving and increase the probability of relapse during abstinence; (2) interact with stress to promote negative affect during abstinence; and (3) contribute to the inability of the alcoholic to control drinking during relapse.

Breese emphasizes that, while the affective pathologies of alcoholism can be manifested more subtly than motor pathologies, they are no less important in contributing to the development and maintenance of alcoholism.

For Townes van Zandt, both affective and physical aspects of alcohol withdrawal were important in motivating him to continue to drink even while drinking was killing him. In fact, affective aspects of alcohol withdrawal probably operate earlier during the course of alcoholism to maintain drinking and to cause relapse.

Breese's work suggests the need for interventions to disrupt the adaptive neural changes associated with kindling of affective components of alcohol withdrawal as well as treatments to minimize negative affect caused by stressful events that increase the probability of relapse during abstinence. His laboratory is currently exploring the contribution of cytokines during abstinence to the negative affect observed following repeated cycles of alcohol exposure. ■



The Director's Column

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

George Breese is the kind of pharmacologist who loves to make discoveries that help people. Although most agree that epileptic seizures kindle, George looked at kindling as a fundamental process involving long term alterations that change brain function. He first discovered that alcohol withdrawal seizures kindle like epileptic seizures. Then he explored whether kindling could occur with negative affect, a vague term that encompasses anxiety, dysphoria, bad feelings, depression and loss of interest in social interaction. This might seem like a small step, but the basis of the seizure kindling hypothesis was that the seizure caused such major adaptations in the brain that the next seizure was more likely. Most animal drinking models do not show seizures during withdrawal. George proposed that loss of alcohol (withdrawal) is the key element rather than the seizure itself.

In collaboration with David Overstreet and Darin Knapp, George found that subtle measures of negative affect, like social interaction, change during alcohol withdrawal in rats. The really unexpected discovery was that this subtle social interaction measure showed increased intensity and duration

(kindling) with multiple drinking-abstinence episodes, but without any seizures. This is particularly exciting in part because it now relates to a more clinical situation.

Relapse during recovery from alcoholism is associated with anxiety, craving, stress and other factors that can be explored using this model. The discovery that stress can mimic an alcohol drinking bout by increasing the negative affect that can induce relapse is very exciting, because it is one of the first instances that couples stress and alcoholism to long-term adaptations in the brain. George is working hard to identify these adaptations and show how they can be re-activated by stress, drinking or other stimuli that might trigger relapse.

Pharmacological studies of agents that can prevent the “kindling” or activation of the negative affect response give insight into its mechanism, as well as providing potential therapeutic approaches to help prevent relapse. This kind of translational work is just what George loves to do. In fact, he proposed a “high risk-high gain” clinical trial that will be headed by Dr. J.C. Garbutt, a Center faculty member. Funded by donations to the Center for Alcohol Studies, the trial will include safe and approved drugs not currently used in alcohol recovery, but used to reduce negative affect-anxiety. The hypothesis is that factors which trigger the kindled negative affect induce relapse and that drugs shown to block the kindled response in animals will block the response in humans, thereby preventing relapse. We are all excited about this translational effort and hope it will be successful in helping people maintain their abstinence. This approach might also delineate new and innovative ways to treat addiction. ■

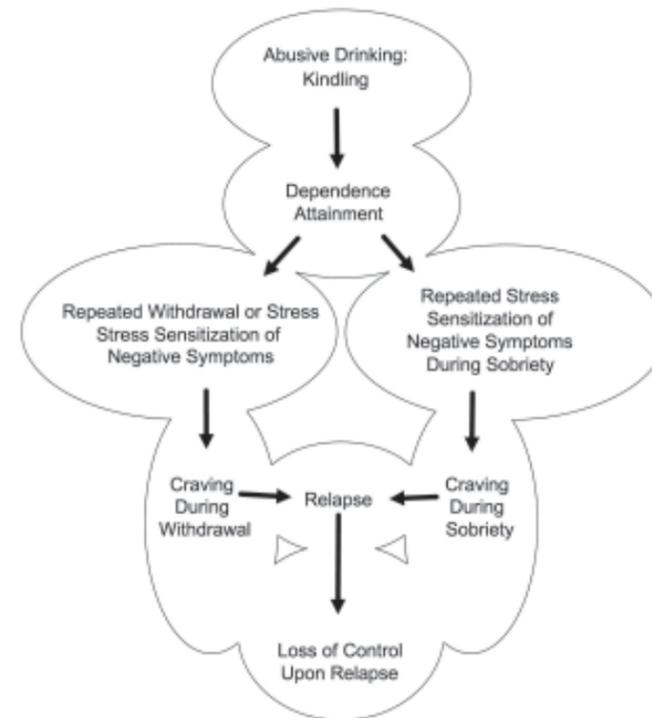


Figure. Schematic representation of the contribution of kindling to the etiology of alcoholism. Adapted from Breese et al. *Psychopharmacology* 2005; 178: 367-380.

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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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Breese Laboratory Advances Kindling Model as Framework for Understanding the Behavioral Pathology of Alcoholism

John T. van Zandt II, son of the Texas blues and folk musician Townes van Zandt, describes the years before his father's death from alcoholism in 1997 at the age of 52:

It was a miserable time...He became so uncontrollable because of his alcoholism that I had to ration his intake to keep him from convulsing and at the same time not too drunk to play. I had to be a chemist of sorts...He blew every third gig and maybe three in a row and we're talking great American music halls where people just got up and walked out, where he never played a note...and we were just wondering how much worse it could get. The answer was plenty worse...A couple of years before he died, he went into treatment 14, 15 times, to serious hospitals with the full detox...mandatory treatment to keep him from dying through withdrawals.

(<http://www.rockzilla.net/rockzilla/ebertowski72.html>)

The young van Zandt's description of progressively worsening alcohol withdrawal is familiar to clinicians who treat alcoholics. It is widely known that physical withdrawal symptoms such as tremors, fever, and convulsions become increasingly severe and frequent as the number of episodes of detoxification increases. Human studies have found increased susceptibility and intensity of seizures in epilepsy with repeated convulsions and have referred to this progressive increase as kindling. In

kindling, repeated stimulation sensitizes brain circuits such that they are more easily activated in response to subsequent stimulation. It is hypothesized that alcohol withdrawal activates brain circuits responsible for seizures and that multiple withdrawals over time cause progressive, adaptive



Breese Lab (Left to Right): George Breese, Ph.D., Kui-Ling Huang, Darin Knapp, Ph.D., Yan Hua Gao, MD, David Overstreet, Ph.D., Katie Jungbluth, Bonita Blake, DVM, Ph.D., Hugh Criswell, Ph.D., Zhen

neural changes that increase the susceptibility of these circuits to activation by subsequent withdrawals. Kindling-associated neural changes appear to be *cumulative*, such that each episode of withdrawal contributes to the state of growing susceptibility, and *persistent*, such that the increased susceptibility is maintained over time.

Dr. George Breese, Professor of Psychiatry and Pharmacology at the Bowles Center for Alcohol Studies, sought to relate this kindling hypothesis to work in his laboratory. With nearly 400 scientific publications to his name and a reputation for tackling scientific

problems elegantly and rigorously, Breese uses animal models to study mechanisms and manifestations of alcohol withdrawal. Breese and his laboratory have advanced the kindling hypothesis by demonstrating that kindling, once thought to underlie only motor aspects of alcohol withdrawal, also appears to underlie affective aspects of alcoholism and alcohol withdrawal. They have also shown that kindling, formerly considered to operate mainly in advanced, severe alcoholism, may begin very early during the course of alcoholism and, in fact, may be a crucial process underlying development of alcohol dependence.

The alcohol withdrawal syndrome is manifested by negative affect, including symptoms such as anxiety and agitation, in addition to motor symptoms such as convulsions. Breese hypothesized that negative affect might be sensitized (kindled) in the way that alcohol-withdrawal seizures are. Working with colleagues Drs. Darin Knapp and David Overstreet, he modeled repeated withdrawals from alcohol by exposing rats to three 5-day regimens of alcohol-containing diet with two days of abstinence between each regimen. They found that rats exposed to repeated withdrawals showed more negative affect in two tests of anxiety-like behavior than rats exposed to only

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Fulton Crews Receives 2006 Bowles Lectureship Award

On April 24, Bowles Center for Alcohol Studies (BCAS) Director Fulton Crews, Ph.D., received the Bowles Lectureship Award for his work in alcohol research.

Established in 1996 by the family of Hargrove Skipper Bowles, the Award honors distinguished researchers who have made significant contributions to our understanding of the causes, prevention and/or treatment of alcoholism and alcohol abuse. Crews is the ninth researcher to receive the award and the first from UNC.

William L. Roper, M.D., MPH, dean of the UNC School of Medicine and CEO of UNC Health Care, presented the award plaque to Crews during the



Fulton Crews (left) with Dean William Roper

event on campus. Both Roper and National Institute on Alcohol Abuse and Alcoholism Director Ting Kai Li, M.D., spoke to a packed room about Crews' accomplishments.

"This award has been given to some of the most imminent scientists in the world today," said Roper. "Fulton Crews has long been a leader on this campus, and it's a pleasure to see him recognized for his national and international leadership in the field of alcohol."

"Dr. Crews has led the center to a level of considerable renown," said Li. "It is a joy to be able to help honor him here today. I can't think of anyone more

deserving of this award."

The award presentation was followed by an hour-long seminar by Crews entitled, "Neurobiological Changes During Alcohol Dependence and Recovery."

Crews, a UNC-CH professor of pharmacology and psychiatry, has led the field in understanding the neurotoxic effects of alcohol on the brain, including cell death and inhibition of neurogenesis. In his 12 years as BCAS director, Crews has established the Center as a world leader in molecular medical research on the mechanisms of alcoholic pathology in the brain, liver and fetus.

"This award is particularly special because it comes from my colleagues. Knowing the others who have received this award and the impact of their work, it's really an honor to be recognized as part of that group," said Crews. ■

The Bowles Center for Alcohol Studies

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www.med.unc.edu/alcohol

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