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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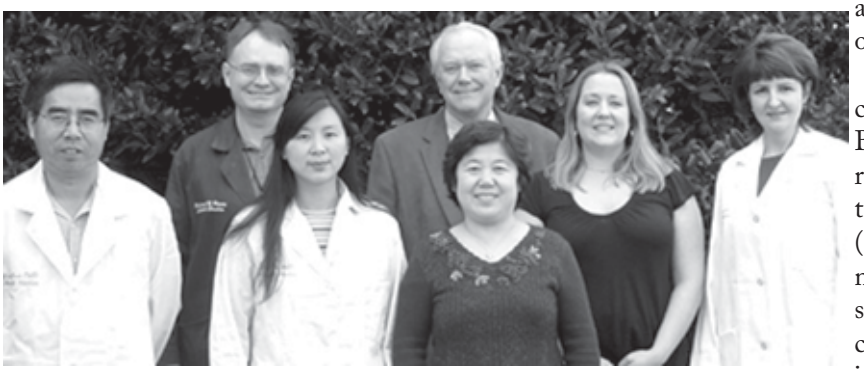
Crews Lab Discovers Inflammatory Mechanisms Underlying Alcohol-Induced Brain Damage

"I don't drink these days. I am allergic to alcohol.....I break out in handcuffs."
-Robert Downey, Jr.

While Robert Downey, Jr.'s statement was made in jest, it encapsulates an earnest opinion often expressed by alcoholics: that alcohol provokes an "allergic reaction" characterized by a unique physiological and psychological sensitivity to alcohol's effects. The idea that an allergic reaction to alcohol underlies alcoholism was first introduced into the medical literature by the New York physician W. D. Silkworth. In his pioneering 1937 paper, "Alcoholism as a Manifestation of Allergy," Silkworth argued that alcoholism is a physical malady with a development and course analogous in many respects to allergies such as hay fever. His conceptualization of alcoholism as an allergic state ran counter to the prevailing view of alcoholism as a moral failing and continues to resonate among today's alcoholics and recovering alcoholics, who still widely cite and discuss Silkworth's work.

In the 1930s, before the advent of neurobiological research on alcohol effects, Silkworth had no means of garnering biological support for his hypothesis of alcoholism as an allergic reaction. Subsequent advances in research technology have made it possible to study biological correlates of alcoholism. Dr. Fulton Crews, alcohol researcher and Director of the University of North Carolina's Skipper Bowles Center for Alcohol Studies, is at the forefront of efforts to elucidate the neurobiology of alcoholism. Crews says that, while Silkworth's concept of alcoholism as a classical allergic reaction has not been fully supported, remarkable parallels between allergic responses and the body's response to alcohol have been revealed. In short, both allergic responses and the body's response to alcohol involve inflammatory processes in which cytokines play key roles. Cytokines constitute a diverse group of proteins that regulate immune responses, inflammation, hormones, wound healing, and communication among cells throughout the body. Only recently have they been studied in the brain. The action of pro-inflammatory cytokines is crucial for defending the body against infections. Anti-inflammatory cytokines and growth factors also contribute to the diverse actions of this large family of mediators.



Crews Lab (Left to Right): Front Row: Jian Zou, PhD, Richard Hanes, Jun He, PhD, Fulton Crews, PhD, Liya Qin, PhD, Tonya Hurst, Olivera Pluzarev, PhD.

Crews' interest in cytokines was sparked by his Bowles Center colleagues' research demonstrating that tumor necrosis factor-α (TNFα), a proinflammatory cytokine released by specific liver cells, contributes to liver disease in alcoholism. Chronic alcohol use causes a leaky gut, with bacteria and ethanol combining to stimulate the liver to make TNFα and other cytokines as part of an inflammatory reaction. Present in excess, TNFα and other cytokines cause cellular toxicity and over time contribute to alcoholic liver disease. Crews, whose primary research focus is alcohol-induced brain degeneration, speculated that cytokines might also contribute to neurodegeneration in alcoholism. Cytokines are produced in the brain by microglia, which are the brain's immune cells. In a study in rats, Crews and his colleagues discovered that a binge alcohol treatment regimen modeling the drinking pattern of human alcoholics in fact caused microglial activation accompanied by persistent increases in the proinflammatory cytokines TNFα, interleukin-1 beta (IL-1β), and monocyte chemotactic protein-1 (MCP-1). These cytokine changes were

Continued on next page

Fulton T. Crews, Ph.D.

Affiliations

Director, Bowles Center for Alcohol Studies; Professor, Departments of Pharmacology and Psychiatry.

Education and Training

Post-doctoral training in pharmacology, National Institutes of Health, Bethesda, MD, 1980;
Ph.D., Pharmacology, University of Michigan, Ann Arbor, 1978;
B.S., Physiology, Syracuse University, NY, 1971.

Recent Publications

Qin, L, Wu, X, Block, ML, Liu, Y, Breese, GR, Hong, JS, Knapp, DJ, **Crews, FT**. Systemic LPS causes chronic neuroinflammation and progressive neurodegeneration. Glia, 55(5): 453-62 (2007).

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Zou, J, **Crews, FT**. CREB and NF-kappaB transcription factors regulate sensitivity to excitotoxic and oxidative stress induced neuronal cell death. Cell Mol Neurobiol, 26(4-6): 383-403 (2006).

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Website

http://www.med.unc.edu/alcohol/faculty/CrewsFT/Crews.htm

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accompanied by binge-induced brain damage. These findings are consistent with Crews' hypothesis that uncontrolled activation of microglia directly releases cytokines that are toxic to neurons.

Knowing that liver cells, like the brain's microglia, overproduce cytokines when exposed to alcohol, Crews hypothesized that the brain might be also exposed to cytokines originating from the liver in individuals who consume excessive alcohol. Liver-originating cytokines such as TNFα are released into the bloodstream to cause inflammation throughout the body. To explore the hypothesis that peripheral TNFα affects inflammation in brain, Crews and his collaborators used the bacterial endotoxin lipopolysaccharide (LPS) to stimulate TNFα production in mice. They found that elevations in TNFα levels in the liver, serum, and brain coincided shortly after LPS administration. However, whereas TNFα levels declined to normal in liver and in serum within a short period of time, TNFα levels remained elevated in the brain for up to 10 months. In another experiment, Crews and his colleagues systemically administered LPS or TNFα to normal mice and to a group of mice bred to genetically lack the TNFα receptor, a receptor previously shown to transport TNFα from serum to brain. In the normal mice, but not in mice lacking the TNFα receptor, systemic administration of LPS or TNFα was associated with activation of microglia; increased levels of pro-inflammatory cytokines, specifically TNFα, MCP-1, and IL-1β, in the brain; and loss of neurons in the substantia nigra, a brain region known to have lots of microglia. These experiments illustrate how inflammation originating outside the brain can trigger persistent brain inflammation that is associated with brain damage. Elevated TNFα in the periphery induced brain TNFα, activated microglia, and caused delayed neurodegeneration. "These results suggest that when TNFα is elevated in serum, the brain is also in trouble," says Crews. "One fascinating aspect of this discovery is that serum cytokine levels return to normal, whereas the brain, once primed by serum TNFα, has elevated proinflammatory cytokine levels for long periods, perhaps forever."

One of the myriad pro-inflammatory actions of TNFα is activation of nuclear factor κB (NF-κB), a transcription factor that regulates genes' production of proteins by binding to particular sites on DNA. NF-κB is a pro-inflammatory transcription factor that causes genes to produce potentially cell-damaging oxidative enzymes such as nicotinamide adenine dinucleotide phosphate-oxidase and cyclooxygenase-2 (COX2), as well as more TNFα and other proinflammatory cytokines. Crews showed that alcohol increased NF-κB DNA-binding activity in brain. Alcohol, proinflammatory cytokines, NF-κB DNA-binding, and oxidative stress were found to interact to promote neurodegeneration contributing to alcohol-associated brain damage as well as other neurodegenerative conditions including Alzheimer's disease and Parkinson's disease. An antioxidant (butylated hydroxytoluene) reduced NF-κB DNA-binding activity and alcohol-induced neurotoxicity both in vitro and in vivo using the binge model of alcohol neurodegeneration. Binge alcohol treatment was associated with microglial activation, increased NF-κB DNA-binding activity, and brain damage. The brain damage was reversed by antioxidant treatment. The results suggest a crucial role of NF-κB in neurotoxicity caused by oxidative stress, including that associated with alcohol, and support the hypothesis that neuroinflammation contributes to alcohol-induced brain damage.

Crews and his colleagues have recently extended their work to humans. In a study with human postmortem brains supplied by the Australia Brain Donor Program, they observed neuroinflammation and increased morphological signs of microglial activation. Furthermore, they found that levels of the proinflammatory cytokine MCP-1 were significantly higher in the brains of alcoholics than the brains of control, moderate-drinking individuals.

Considered in aggregate, Crews' findings suggest that excessive alcohol consumption sets off a spreading cytokine process (Figure). Alcohol disrupts cytokines both within organs and between organs. For example, alcohol perpetuates inflammation within the brain when it induces NF-κB DNA-binding activity, which activates inflammatory mediators that stimulate

further increases in NF-κB DNA-binding activity and trigger various inflammatory cascades. Alcohol perpetuates inflammation between organs as when TNFα produced in the liver affects inflammatory responses in the brain (Figure). Crews found that the liver makes anti-inflammatory cytokines in response to alcohol that in time suppress proinflammatory responses, whereas ethanol suppresses proinflammatory cytokines in brain, an effect that might contribute to the previously observed pro-longed increases in brain TNFα. Although more research needs to be done, it is possible that increased anti-inflammatory cytokines could contribute to the health benefits associated with low levels of drinking.

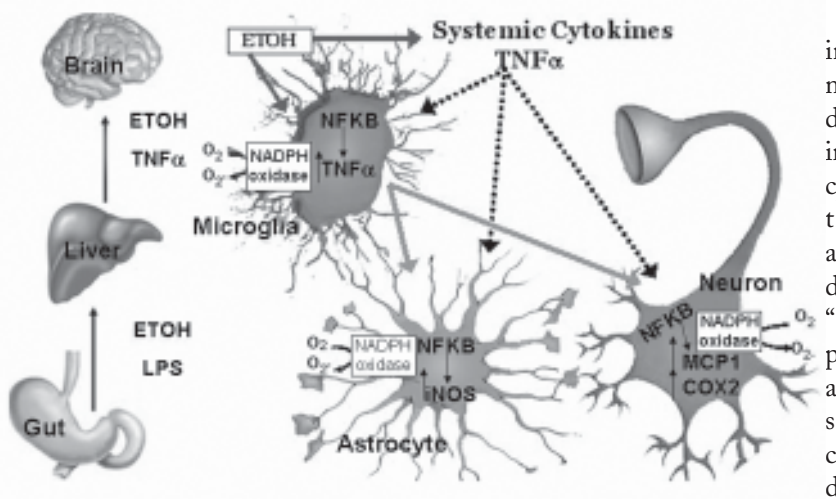

Figure: Ethanol increases systemic and brain cytokines. Alcohol (ethanol-ETOH) is consumed orally, enters the gut and makes the gut leaky allowing endotoxin (lipopolysaccharide-LPS) to enter the circulation. LPS and ethanol activate the liver to produce cytokines such as TNFα. Ethanol and TNFα enter the brain and increase brain cytokine synthesis. Within brain, microglia, astrocytes and neurons respond by altering gene expression that contributes to alcoholic neurodegeneration.

"Many physiological and psychological aspects of alcoholism could be secondary to the cytokine changes we have discovered," notes Crews. "Understanding cytokines could provide new diagnostic and therapeutic approaches to many chronic diseases, particularly those known to be influenced by alcohol." ■

ASAP Clinic- A National Model for Alcohol and Substance Abuse Treatment

The Alcohol and Substance Abuse Program (ASAP) at UNC uses cutting-edge approaches based on the most current and relevant research on alcoholism and substance abuse. ASAP utilizes research-based protocols, and each addiction therapist on staff is trained in motivational interviewing, cognitive-behavioral therapies and psychosocial strategies to ensure medication compliance. The program, part of UNC Healthcare, the Bowles Center for Alcohol Studies and the Department of Psychiatry, specializes in individualized treatment based on the unique needs, motivation and personal goals of each patient.

ASAP Staff (Left to Right): Ben Lancaster, LPC, Bill Renn, LCSW, LCAS, Tom Watkins, LCAS, Arleta Brooks, CNA, Kathy Grace, LPC, J.C. Garbutt, MD.

"ASAP has the ability to treat individuals who need to commit to lifelong abstinence, as well as those patients who are much more ambivalent about the damage that their alcohol or drug addiction is causing them," said Bill Renn, ASAP Director and Associate Professor of Psychiatry at UNC. "Our models of care and our approaches are based on the latest research and literature in the field, and I consider this to be a national model for care based on the experience and expertise of the staff."

Over the past several years, ASAP has been involved in a number of clinical trails. Its current research studies focus on the use of pharmacotherapy to treat alcohol and drug dependence. One study measures the efficacy of the drug Aripiprazole in conjunction with the use of weekly, psychosocial treatment sessions. The other study compares those with alcohol dependence who prefer sweets to those who do not and their response to Naltrexone.

"These research efforts have been rewarding to the staff and have been published in two major journals. Although there are no medications dispensed or available at this clinic, our efforts led to the FDA approval of long-acting injectable naltrexone for the treatment of alcohol dependence," said Renn.

The Program is also heralding new initiatives that will make treatment for patients even more convenient and accessible. In February, ASAP added a Day Treatment Group that meets four days a week, Monday through Thursday, from 1:30-3 p.m. The treatment sessions focus on a curriculum that includes gaining and maintaining abstinence, relapse prevention, key coping and refusal skills, spirituality, meditation, and other science-based interventions.

"We already have a night group in place but have growing numbers of patients who are unable to join us in the evening." said Renn. "We wanted to offer an alternative for those patients."

In addition to the day and evening groups, a walk-in clinic is in the planning stages. Renn expects that the new walk-in clinic will begin in early April. A Brief Intervention Model, along with a clinical interview, will be made available to walk-ins on Fridays from 10 a.m. until 2 p.m. This new walk-in format will operate on a first come, first served schedule and will allow ASAP staff to meet and evaluate even more patients who seek treatment for addiction. "I encourage everyone who is thinking about treatment to come in. Let's start the conversation," Renn said.

Renn and his staff, which consists of four masters-level addiction therapists, work incredibly well as a team and have treated hundreds of patients since ASAP began in 1998. Treatment lasts anywhere from three months up to a year and ranges from intensive outpatient to more traditional outpatient clinic visits for both substance abuse and mental health.

ASAP also works very closely with the UNC Department of Psychiatry's Substance Abuse Clinic, headed by J.C. Garbutt, M.D. Garbutt, also the medical director for ASAP, is an expert in the pharmacological treatment of alcohol dependence, as well as a faculty member of the Bowles Center for Alcohol Studies.

While ASAP does not offer free services, every effort is made to treat those who seek help. UNC Health Care accepts most forms of insurance, Medicare and Medicaid, and financial counselors will work individually with each patient to develop a manageable payment plan. "This is not a crisis service," Renn stressed. "Those individuals who are in medical or psychiatric crisis should go directly to UNC Hospital."

"We really work together attempting to treat, prevent and cure alcoholism and drug addiction. We would like treatment to be available for everyone who needs it," said Renn. "Our door is open, and we're not going to turn anyone away."
For more information or to make an appointment with ASAP, call (919) 966-6039/ (888) 457-7457, or visit http://www.med.unc.edu/alcohol/asap. ■

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The Director's Column

A. Leslie Morrow, Ph.D.
Associate Director,
Bowles Center for
Alcohol Studies

Dr. Fulton Crews' brilliance can be attributed in part to his understanding that human beings are not just a conglomerate of molecules and cells but complex organisms with integrated organ, immune and endocrine systems. Alcohol effects on all these systems will ultimately impact many molecules and cells throughout the body. Hence, systemic effects of alcohol on the entire body play a role in the ultimate effects of alcohol on brain cells – including the ability of alcohol to kill brain cells. Perhaps leading the Bowles Center for Alcohol Studies, where investigators research alcohol actions on brain, liver, pancreas, fetus, the endocrine system and the immune system, has contributed to Crews' insights. Alternatively, I suspect that he assembled this diverse group of researchers to study alcohol actions across so many systems of the body for the very purpose of discovering how the complex systemic and molecular roles of alcohol go awry in the disease of alcoholism.

This integration of research across systems, organs, brain regions, human development and the progression to alcoholism is the hallmark of research in the Bowles Center for Alcohol Studies. Dr. Fulton Crews has led this Center to promote such integration and has brought together a team of researchers determined to find the causes and successful treatments for alcoholism in our lifetime.

The Crews Lab is likely to find how preventing the proinflammatory effects of alcohol can prevent the development of alcoholism and promote recovery by preventing relapse. His lab has shown that heavy alcohol use can kill brain cells, prevent neurogenesis and the survival of new brain cells, and promote inflammation across organ systems that persists in the brain. Inflammation may be the key to many diseases in many organs, as well as the endocrine and immune systems, that disrupts normal function and leads to the demise of the organism – the human being. Thus, the importance of Crews' research extends far beyond the effects of alcohol on brain cells and molecules.

The faculty of the Bowles Center for Alcoholism, along with their advisors and consultants recognized the achievements and brilliance of Fulton Crews by awarding him the 2006 Bowles Lectureship Award. We are proud of his leadership of our Center, and we are proud to work with a great coach towards the championship in the tournament to reduce human suffering from alcoholism. ■

The Bowles Center for Alcohol Studies

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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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A. Leslie Morrow, Ph.D., Editor-in-Chief; Elizabeth Thomas, Managing Editor; Jane Saiers, Ph.D., Science Writer

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