BIOGRAPHICAL SKETCH

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NAME Clyde W. Hodge	POSITION TITLE Professor, Departments of Psychiatry and Pharmacology
eRA COMMONS USER NAME (credential, e.g., agency login)	

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	MM/YY	FIELD OF STUDY
University of Alabama, Birmingham, AL	B.S.	1986	Psychology/Computer Sci.
Auburn University, AL	M.S.	1989	Experimental Psychology
Auburn University, AL	Ph.D.	1991	Behav. Pharmacology
University of Washington, Seattle (with Dr. Hank Samson)	Postdoc	'91-92	Neuroscience

A. Personal Statement

I have conducted preclinical alcohol and drug abuse research for 25 years with continuous NIAAA funding since 1995. My laboratory focuses on understanding how alcohol alters neural processes to gain control over the individual via altered reinforcement mechanisms. Using rodent models, we have identified specific neural systems that regulate alcohol-seeking behavior and evaluate co-morbid neuropsychiatric conditions such as anxiety and depression. Recently, we have utilized unbiased high-throughput proteomic screens, to discover the spectrum of neural proteins that are altered by alcohol use by adults and adolescents. Protein targets in specific brain regions are validated for functional involvement in alcohol self-administration using site-specific microinjection strategies. At the mechanistic level, our studies have identified glutamate-linked receptors (e.g., NMDA, mGluR5, AMPA) and associated signaling pathways (e.g., PKC, ERK, CaMKII) as key targets of that regulate alcohol reinforcement. Recently, we have incorporated optogenetics and electrophysiological measures in our studies via training and collaboration within the UNC Alcohol Center Core, of which Dr. Hodge is the Director. By delineating how alcohol alters protein networks that, in turn, regulate drug-seeking behavior, we hope to elucidate novel neural mechanisms that influence the development of addiction.

B. Positions and Honors

Positions and Employment

1991-92 Postdoctoral Fellow, Dept. of Psychiatry, Univ. of Washington, Seattle (with Dr. Hank Samson)
1992-93 Research Scientist, Alcohol and Drug Abuse Institute, University of Washington, Seattle
1993-95 Res Associate, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC
1995-97 Asst Professor, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC
1997-2001 Assistant Professor, Dept. of Neurology, Gallo Center, University of California, San Francisco
2001-2001 Assoc Professor, Dept. of Neurology, University of California, San Francisco
2001-2006 Assoc Professor, Depts. Psychiatry and Pharmacology, Univ of North Carolina at Chapel Hill
2006- Professor, Depts. Psychiatry and Pharmacology, Univ of North Carolina at Chapel Hill

Selected Positions and Appointments

2003 – Field Editor, *Alcoholism Clinical and Experimental Research*
2011 – Member, NIAAA Study Section, Neuroscience (AA-4)
2003 – 2007 Member, CSR Study Section, Neurotoxicology and Alcoholism (NAL)
2005 – 2008 Research Society on Alcoholism, Research Priorities Committee
2003 – 2007 Board of Directors, Research Society on Alcoholism
2008 – 2009 Member, Program Committee, Research Society on Alcoholism
2009 – 2010 Co-Chair, Program Committee, Research Society on Alcoholism

Selected Honors and Awards

1990-91 National Research Service Award, National Institute on Alcohol Abuse and Alcoholism
1996 Distinguished Young Investigator Award, Research Society on Alcoholism
2010 Faculty-to-Faculty Mentoring Award, UNC Provost and Carolina Women's Leadership Council
2011 Junior Faculty Mentoring Award, UNC Department of Psychiatry

C. Selected Contributions to Science

1. ***Mesolimbic Dopamine Systems Regulate the Reinforcing Effects of Alcohol***. Alcohol addiction is a complex degenerative condition that begins with repeated binge/intoxication episodes that are primarily controlled by the positive reinforcing effects of the drug. My initial research in the alcohol field began as a postdoc at the University of Washington in Seattle with my mentor and friend, Dr. Hank Samson in 1991. Using Hank's sucrose fading procedure combined with site-specific microinjection techniques in rats, our work addressed the seminal question of whether mesolimbic dopamine mechanistically regulates the positive reinforcing effects of alcohol. We showed that enhanced dopamine activity in the nucleus accumbens escalates operant alcohol self-administration. This was the first evidence that the brain's reward pathway functionally escalates alcohol self-administration via dopamine. We also showed that dopamine and GABA receptor activity in the accumbens, VTA and PFC are required for the reinforcing effects of alcohol. We established critical analyses, including assessing the ***onset***, ***maintenance***, and ***termination*** of operant alcohol self-administration and published a total of 17 papers addressing fundamental mesolimbic mechanisms of alcohol reinforcement.

    a. Hodge CW, Haraguchi M, Samson HH. Microinjections of dopamine agonists in nucleus accumbens increase ethanol reinforced responding. Pharmacol Biochem Behav 43:249 254; 1992.
    b. Samson HH, Tolliver GT, Haraguchi M, Hodge CW. Alcohol self-administration: role of mesolimbic dopamine. In: Samson HH, Kalivas PW, (eds), The Neurobiology of Drug and Alcohol Addiction. New York: Ann. NY Acad. Sci., 242 253; 1992.
    c. Hodge CW, Haraguchi M, Erickson HL, Samson HH. Microinjections of quinpirole in the ventral tegmentum decrease ethanol reinforced responding. Alcohol Clin Exp Res 17:370 375; 1993.
    d. Hodge CW, Chappelle A, Samson HH. Dopamine receptors in the medial prefrontal cortex influence ethanol and sucrose reinforced responding. Alcohol Clin Exp Resh 20:1631-1638; 1996.
    e. Hodge, CW, Samson, HH, Chappelle, AM: Alcohol self-administration: further examination of the role of dopamine receptors in the nucleus accumbens. Alcohol Clin Exp Res 21:1083-1091; 1997.

2. ***PKC-epsilon Regulates Alcohol Sensitivity, Interaction with GABA-A Receptors, and Self-Administration***. My first tenure track faculty position began in 1997 at UCSF in the Neurology Department with an appointment in the Gallo Center (Ivan Diamond, Director). At that time, Ivan, Dr. Adrienne Gordon, and Dr. Bob Messing were investigating the effects of alcohol on the activity and function of PKC isoforms in cell culture. With help from the Gladstone Institute and private funding from the Gallo family, a PKC-epsilon knockout mouse was generated. In a variety of studies, my laboratory discovered that PKC-epsilon regulates alcohol and benzodiazepine sensitivity of GABAA receptors, which had major implications in alcohol self-administration and other responses. Accordingly, PKC-epsilon mice self-administer less alcohol, are more sensitive to the sedative and activating effects of alcohol, and show reduced withdrawal severity. Moreover, my laboratory discovered that PKC-epsilon mice show a dramatically blunted mesolimbic dopamine response to alcohol. Overall, these were the first studies to identify the behavioral and in vivo relevance of PKC-epsilon to the addictive properties of alcohol.

    a. Hodge CW, Mehmert K, Kelley SP, McMahon T, Haywood A, Olive MF, Wang D, Sanchez-Perez AM, Messing RO. Supersensitivity to allosteric GABAA modulators and alcohol in mice lacking PKCε. Nature Neuroscience 2, 997-1002, 1999.
        - Featured with commentary: Kalyani Narasimhan K. Creating teetotaler mice. Nature Neuroscience 2, p. 935, 1999.
    b. Khasar S, Lin Y-H, Martin A, Dadgar J, McMahon T, Hundle B, Aley K, Isenberg W, Green P, Hodge CW, Levine J, & Messing R. A novel nociceptor signaling pathway revealed in protein kinase C epsilon mutant mice. Neuron 24: 253-260; 1999.
    c. Olive MF, Mehmert KK, Messing RO, Hodge CW. Reduced operant ethanol self-administration and in vivo mesolimbic dopamine responses to ethanol in PKC-epsilon deficient mice. European Journal of Neuroscience 12: 4131-4140; 2000.
    d. Olive MF, Hodge CW. Co-localization of PKCe with various GABAA and NMDA receptor subunits in the mesolimbic system. NeuroReport 11: 683-687; 2000.
    e. Olive MF, Mehmert KK, Nannini MA, Camarini R, Messing RO, Hodge CW. Reduced ethanol withdrawal severity and altered withdrawal-induced c-fos expression in various brain regions of mice lacking protein kinase C-epsilon. Neuroscience 103:171-179; 2001.

3. ***Novel Molecular Mechanisms of Anxiety and Depression***. Based on our work with PKC-epsilon and GABAA receptors, I put forward the hypothesis that the kinase may influence anxiety-like behavior (via enhanced GABAA activity). As part of an ABMRF and State of California funded project, we showed that PKC-epsilon null mice exhibit an anxiolytic phenotype that is mediated by GABAA receptor activity. We also showed, in collaboration with the Baekkeskov lab, that GAD-65 null mice exhibit heightened anxiety-like behavior. We also showed that loss of the 5-HT3A molecular subunit produces an anxiolytic phenotype in mice. These studies were the first to identify these novel molecular mechanisms of anxiety and suggest new neural targets and treatment strategies for the medical management of anxiety.
    a. Kash SF, Tecott LH, Hodge C, Baekkeskov S. Increased anxiety and altered responses to anxiolytics in mice deficient in the 65 kDa isoform of glutamic acid decarboxylase (GAD65). Proceedings of the National Academy of Science, Vol. 96, Issue 4, 1698-1703; 1999.
    b. Hodge CW, Raber J, McMahon T, Walter H, Sanchez-Perez AM, Olive MF, Morrow AL, Messing RO. Decreased anxiety, reduced stress hormones, and neurosteroid sensitivity in mice lacking protein kinase C - ε. The Journal of Clinical Investigation 110: 1003-1010; 2002.
        - Featured with commentary: Gordon JA. Anxiolytic drug targets: beyond the usual suspects. J. Clin. Invest. 110:915–917 (2002).
    c. Kelley SP, Bratt AM, Hodge CW. Targeted gene deletion of the 5-HT3A receptor subunit produces an anxiolytic phenotype in mice. European Journal of Pharmacology, 461:19-25; 2003.
    d. Stevenson JR, Schroeder JP, Nixon K, Besheer J, Crews FT, Hodge CW. Abstinence from alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. Neuropsychopharmacology 34, 1209–1222; 2009.
        - Cover article with featured image.

4. ***Neural Basis of the Interoceptive (Discriminative Stimulus) Effects of Alcohol***. My first R01 (awarded in 1994) sought to determine if the discriminative stimulus effects (subjective effects) of alcohol are regulated by GABAA and/or NMDA receptors in specific limbic brain regions. At the time, it was known that systemic GABAergics and NMDA antagonists would substitute for systemic alcohol in drug discrimination models. However, there was no information regarding brain regional regulation of this critical addiction-linked property of alcohol. We are the only laboratory to address this question to date and have shown, for instance, that a microinjection of the GABAA agonist muscimol in the nucleus accumbens substitutes fully for a full systemic dose of alcohol (1 g/kg). We have extended this work into several limbic brain regions, used dual-area infusions to demonstrate circuit regulation, and included our new focus on mGlu5 receptors and conducted cfos-mapping studies to identify brain regional activation during alcohol discrimination. Overall, this work shows that the perception of alcohol (interoceptive stimulus) and self-administration are regulated by overlapping mechanisms and neural circuits, suggesting that the perception of alcohol regulates, or interacts with, self-administration. Accordingly, we developed a procedure to assess the discriminative stimulus effects of self-administered alcohol and found co-regulation of discrimination and self-administration by GABAA and NMDA receptors. This work underscores the critical importance of the subjective effects of alcohol.
    a. Hodge CW. Comparison of the discriminative stimulus function of ethanol following intracranial and systemic administration: evidence of a central mechanism. Pharmacology Biochemistry and Behavior 47:743 747; 1994.
    b. Hodge CW, Cox AA. The discriminative stimulus effects of ethanol are mediated by NMDA and GABAA receptors in specific limbic brain regions. Psychopharmacology 139:95-107; 1998.
    c. Hodge CW, Cox AA, Bratt AM, Camarini R, Iller K, Kelley SP, Mehmert KK, Nannini MA, Olive MF. Besheer J, Cox AA, Hodge CW. Co-regulation of ethanol discrimination by the nucleus accumbens and amygdala. Alcohol Clin and Experimental Research, 27:450-456; 2003.
    d. Besheer J, Hodge CW. Pharmacological and anatomical evidence for an interaction between mGluR5 and GABAA α1 containing receptors in the discriminative stimulus effects of ethanol. Neuropsychopharmacology 30:747-757; 2005.
        - Cover article with featured image.

5. ***Novel Molecular Mechanisms Alcohol Self-Administration and Relapse***. The main purpose of my research is to ***identify*** and ***validate*** novel mechanisms of the positive reinforcing effects of alcohol. Positive reinforcement is required for the etiology of addiction and may subserve initial adaptations that lead to escalated drug use. Our work on this project (Molecular Mechanisms of Ethanol Reinforcement) has focused on glutamate receptor systems and downstream intracellular signaling pathways. We have moved the field forward in our understanding of metabotropic glutamate receptor regulation of alcohol self-administration, discrimination, and acute response (about 20 publications) and recently extended our efforts to include AMPA-type glutamate receptors (renewal focus) due to their prominent role in neuroplasticity and the lack of information in the field regarding AMPA regulation of alcohol self-administration. We have shown that glutamate signaling regulates self-administration and relapse via protein kinase signaling (ERK and CaMKII) in the amygdala and other limbic reward-associated brain regions. We are especially excited about our recent discoveries indicating that the AMPAR-CaMKII signaling pathway is both required for alcohol reinforcement and able to promote escalated self-administration. This bidirectional modulation is a strong indication of a mechanistic biological system that may underlie escalated alcohol intake that occurs during the initial stages of addiction when the positive reinforcing effects of alcohol predominate. This concept forms much of the basis for our continuing (proposed) work.
    a. Besheer J, Grondin JJM, Salling MC, Spanos M, Stevenson RA, Hodge CW. Interoceptive effects of alcohol require mGlu5 receptor activity in the nucleus accumbens. The Journal of Neuroscience 29(30):9582-9591; 2009.
    b. Cannady R, Fisher KR, Durant B, Besheer J, Hodge CW. Enhanced AMPA receptor activity Increases operant alcohol self-administration and cue-Induced reinstatement. Addiction Biology 18(1):54-65; 2013
    c. Salling MC, Faccidomo SP, Li C, Psilos K, Galunas C, Spanos M, Agoglia AE, Kash TL, Hodge CW. Moderate alcohol drinking and the amygdala proteome: Identification and validation of CaMKII as a novel molecular mechanism of the positive reinforcing effects of alcohol. Biological Psychiatry [epub ahead of print]; 2014.
    d. Agoglia AE, Holstein SE, Reid G, Hodge CW. CaMKIIα-GluA1 activity underlies vulnerability to adolescent binge alcohol drinking. Alcohol Clin Exp Res, in press, 6/16/2015.