BIOGRAPHICAL SKETCH

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NAME: Hodge, Clyde W.

eRA COMMONS USER NAME (credential, e.g., agency login): chodge

POSITION TITLE: Professor, Departments of Psychiatry and Pharmacology

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

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Alabama, Birmingham, AL	BS	05/1986	Psychology/Computer Sci
Auburn University, Auburn, AL	MS	1989	Exp Psychology
Auburn University, Auburn, AL	PHD	1991	Behavioral Pharmacology
University of Washington, Seattle, WA	Postdoc	1992	Neuroscience

A. Personal Statement

I serve three roles on this P60 ARC renewal application: co-PI of Research Component 1 (CP1), PI of the Scientific Resource Core (SRC), and member of the Administrative Core as co-Scientific Director. As an established investigator in the alcohol research field, I have conducted preclinical alcohol research for about 30 years with continuous independent NIAAA funding since 1995. My research is primarily aimed at understanding how alcohol gains control over neural systems to drive alcohol-seeking behavior. In recent years, we have focused on elucidating the mechanistic role of excitatory glutamate receptors (e.g., AMPA, mGluR5) and their molecular signaling pathways (e.g., CAMKII, ERK1/2) in the positive reinforcing effects of alcohol. I hope that, ultimately, this preclinical work will help guide the field toward novel pharmacotherapeutic approaches to treat problems associated with AUD. In this continuing P60 ARC project, Drs. McElligott, Faccidomo and myself will extend our prior work on initial non-dependent alcohol use by taking a new focus on discovering how alcohol dependence targets excitatory AMPAR expression and synaptic activity in the BLA→NAcb pathway to produce escalated alcohol self-administration, which is a hallmark pathology of AUD. We will also elucidate the impact of alcohol dependence on novel PDZ domain proteins that regulate AMPAR function, and utilize CRISPR technology to conduct mechanistic behavioral studies. This approach utilizes the SRC to extend our capacity and engage in collaborative efforts with other components to address the center-wide focus on excitatory / inhibitory (E/I) balance. By taking this thoroughgoing molecular, physiological, behavioral, and circuit-based approach, I feel strongly that each aim of this project will be able to make an important, stand-alone, contribution to the field. Our research team is exceptionally well-qualified to conduct these multidisciplinary studies and I am excited to play a part. As PI of the SRC, I will continue to oversee all aspects of Core functioning including scientific services, personnel, facilities, and budgets with the goal of ensuring timely and successful completion of the collaborative aims of this P60 project. Finally, as co-Scientific Director (Admin Core), I will continue in this role to assist Dr. Kash (PI) and Morrow (co-PI) with all administrative functions, including evaluation of scientific progress and allocation of resources to achieve the shared goals of the center. In each of these roles, I will promote our collaborative efforts with the goal of enhancing the significance and integrative impact of each research project to make the whole of the UNC ARC greater than the sum of its parts.

Ongoing and recently completed projects that are relevant to this application:

R01 AA028782, NIAAA
HODGE, CLYDE (PI)
05/10/21-03/31/2026
Novel mechanism of alcohol self-administration and relapse

5P60AA011605-22; Sub-Project ID: 5443, NIAAA
HODGE, CLYDE (PI)
12/01/17-11/30/22
Limbic Glutamatergic Circuits in Ethanol Self-Administration (Component 1)

5P60AA011605-22; Sub-Project ID: 5440, NIAAA
HODGE, CLYDE (PI)
12/01/17-11/30/22
Integration of Molecular and Neurocircuit Pathologies Across Stages of Addiction (Resource Core)

R37 AA014983 , NIAAA
HODGE, CLYDE (PI)
07/01/16-06/30/21
Molecular Mechanisms of Ethanol Reinforcement

Citations that highlight experience, qualifications, and collaborative efforts within the ARC:

1. Hoffman JL, Faccidomo S, Saunders BL, Taylor S, Kim M, Hodge CW. Inhibition of AMPA receptors containing TARP γ-8 with JNJ-55511118 shows preclinical efficacy for pharmacotherapeutic treatment of chronic repetitive alcohol self-administration, Alcohol Clin Exp Res 45, 1424-1435 (2021). PMID: 34086361; PMCID: PMC8336716
2. Faccidomo S, Cogan ES, Hon OJ, Hoffman JL, Saunders BL, Eastman VR, Kim M, Taylor S, McElligott ZA, Hodge CW. Calcium-Permeable AMPA Receptor Activity and GluA1 Trafficking in the Basolateral Amygdala Regulate Operant Alcohol Self-Administration, Addiction Biology, in press (5/2021). PMID: 34086361
3. Agoglia AE, Zhu M; Douglass E, Hanback T, Tella J, Ying R; Hodge CW; Herman M. Sex-specific plasticity in CRF regulation of inhibitory control in central amygdala CRF1 neurons after chronic voluntary alcohol drinking. Addiction Biology, in press (6/2021). PMID: 34086361
4. Cannady R, Fisher KR, Graham C, Crayle J, Besheer J, Hodge CW. Potentiation of amygdala AMPA receptor activity selectively promotes escalated alcohol self-administration in a CaMKII-dependent manner. Addict Biol. 2017 May;22(3):652-664. PMID: 26742808 PMCID: PMC4935658.

B. Positions, Scientific Appointments, and Honors

Positions

1977 - 1986	Computer Operations Supervisor / Programmer Analyst, AmSouth Bank, NA, Birmingham, AL
1989 - 1991	Instructor, Auburn University, Department of Psychology, Auburn, AL
1991 - 1992	Postdoctoral Fellow, University of Washington, Seattle, WA
1992 - 1993	Research Scientist, Alcohol and Drug Abuse Institute, Univ of Washington, Seattle, WA
1993 - 1995	Research Assoc, Wake Forest Univ., Dept of Physiology/Pharmacology, Winston-Salem, NC
1995 - 1997	Asst Professor, Wake Forest Univ., Dept of Physiology/Pharmacology, Winston-Salem, NC
1997 - 2001	Asst Professor, UCSF, Department of Neurology, Gallo Research Center, San Francisco, CA
2001 - 2001	Assoc Professor, UCSF, Department of Neurology, Gallo Research Center, San Francisco, CA
2001 - 2006	Assoc Professor, UNC Departments of Psychiatry and Pharmacology, Chapel Hill, NC
2001 -	Member, Bowles Center for Alcohol Studies, UNC Chapel Hill
2006 -	Professor, UNC, Departments of Psychiatry and Pharmacology, Chapel Hill, NC

Selected Scientific Appointments

2003 -	Director, Scientific Resource Core; UNC P60 Alcohol Research Center
2003 -	Field Editor, Alcoholism Clinical and Experimental Research
2003 - 2007	Member, Neurotoxicology and Alcohol Study Section (NAL), NIH Center for Scientific Review
2003 - 2007	Board of Directors, Research Society on Alcoholism
2005 -	Scientific Advisory Committee, Auburn University
2011 - 2016	Member, Neuroscience Study Section AA-4 , NIAAA
1991 -	Member, Research Societies including: RSA and SFN

Selected Honors

1996 Early Career Investigator Award, Research Society on Alcoholism
2010 Faculty-to-Faculty Mentoring Award, Carolina Women's Leadership Council
2011 Faculty Mentoring Award, UNC School of Medicine
2013 - 2021 NIH MERIT Award (R37), NIAA

C. 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 mechanisms of alcohol reinforcement.

    a. 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. 1997 Sep;21(6):1083-91. PubMed PMID: 9309321.
    b. Hodge CW, Chappelle AM, Samson HH. Dopamine receptors in the medial prefrontal cortex influence ethanol and sucrose-reinforced responding. Alcohol Clin Exp Res. 1996 Dec;20(9):1631-8. PubMed PMID: 8986215.
    c. Samson HH, Hodge CW, Tolliver GA, Haraguchi M. Effect of dopamine agonists and antagonists on ethanol-reinforced behavior: the involvement of the nucleus accumbens. Brain Res Bull. 1993;30(1-2):133-41. PubMed PMID: 8093596.
    d. Hodge CW, Samson HH, Haraguchi M. Microinjections of dopamine agonists in the nucleus accumbens increase ethanol-reinforced responding. Pharmacol Biochem Behav. 1992 Sep;43(1):249-54. PubMed PMID: 1357676.

2. 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 have shown that a microinjection of the GABAA agonist muscimol in the nucleus accumbens substitutes fully for a full systemic dose of alcohol (1 g/kg) and extended this work into several limbic brain regions. 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. Besheer J, Hodge CW. Pharmacological and anatomical evidence for an interaction between mGluR5- and GABA(A) alpha1-containing receptors in the discriminative stimulus effects of ethanol. Neuropsychopharmacology. 2005 Apr;30(4):747-57. PubMed PMID: 15549054; PubMed Central PMCID: PMC2892057.
    b. Besheer J, Cox AA, Hodge CW. Coregulation of ethanol discrimination by the nucleus accumbens and amygdala. Alcohol Clin Exp Res. 2003 Mar;27(3):450-6. PubMed PMID: 12658110.

c. Hodge CW, Cox AA. The discriminative stimulus effects of ethanol are mediated by NMDA and GABA(A) receptors in specific limbic brain regions. Psychopharmacology (Berl). 1998 Sep;139(1-2):95-107. PubMed PMID: 9768547.

d. Hodge CW. Comparison of the discriminative stimulus function of ethanol following intracranial and systemic administration: evidence of a central mechanism. Pharmacol Biochem Behav. 1994 Mar;47(3):743-7. PubMed PMID: 8208795.

3. 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. Olive MF, Mehmert KK, Messing RO, Hodge CW. Reduced operant ethanol self-administration and in vivo mesolimbic dopamine responses to ethanol in PKCepsilon-deficient mice. Eur J Neurosci. 2000 Nov;12(11):4131-40. PubMed PMID: 11069609.

   b. Olive MF, Hodge CW. Co-localization of PKCepsilon with various GABA(A) receptor subunits in the mouse limbic system. Neuroreport. 2000 Mar 20;11(4):683-7. PubMed PMID: 10757500.

   c. Hodge CW, Mehmert KK, Kelley SP, McMahon T, Haywood A, Olive MF, Wang D, Sanchez-Perez AM, Messing RO. Supersensitivity to allosteric GABA(A) receptor modulators and alcohol in mice lacking PKCepsilon. Nat Neurosci. 1999 Nov;2(11):997-1002. PubMed PMID: 10526339.

   d. Khasar SG, Lin YH, Martin A, Dadgar J, McMahon T, Wang D, Hundle B, Aley KO, Isenberg W, McCarter G, Green PG, Hodge CW, Levine JD, Messing RO. A novel nociceptor signaling pathway revealed in protein kinase C epsilon mutant mice. Neuron. 1999 Sep;24(1):253-60. PubMed PMID: 10677042.

4. 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. Stevenson JR, Schroeder JP, Nixon K, Besheer J, Crews FT, Hodge CW. Abstinence following alcohol drinking produces depression-like behavior and reduced hippocampal neurogenesis in mice. Neuropsychopharmacology. 2009 Apr;34(5):1209-22. PubMed PMID: 18563059; PubMed Central PMCID: PMC2844649.

   b. Kelley SP, Bratt AM, Hodge CW. Targeted gene deletion of the 5-HT3A receptor subunit produces an anxiolytic phenotype in mice. Eur J Pharmacol. 2003 Feb 7;461(1):19-25. PubMed PMID: 12568911.

   c. Hodge CW, Raber J, McMahon T, Walter H, Sanchez-Perez AM, Olive MF, Mehmert K, Morrow AL, Messing RO. Decreased anxiety-like behavior, reduced stress hormones, and neurosteroid supersensitivity in mice lacking protein kinase Cepsilon. J Clin Invest. 2002 Oct;110(7):1003-10. PubMed PMID: 12370278; PubMed Central PMCID: PMC151152.

   d. 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. Proc Natl Acad Sci U S A. 1999 Feb 16;96(4):1698-703. PubMed PMID: 9990087; PubMed Central PMCID: PMC15565.

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 recent work 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 (more than 20 publications) and recently extended our efforts to include AMPA-type glutamate receptors 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.

1. Cannady R, Fisher KR, Graham C, Crayle J, Besheer J, Hodge CW. Potentiation of amygdala AMPA receptor activity selectively promotes escalated alcohol self-administration in a CaMKII-dependent manner. Addict Biol. 2017 May;22(3):652-664. PubMed PMID: 26742808; PubMed Central PMCID: PMC4935658.
2. 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 Calcium/Calmodulin Dependent Kinase II and AMPA Receptor Activity as Novel Molecular Mechanisms of the Positive Reinforcing Effects of Alcohol. Biol Psychiatry. 2016 Mar 15;79(6):430-42. PubMed PMID: 25579851; PubMed Central PMCID: PMC4417085.
3. Faccidomo S, Reid GT, Agoglia AE, Ademola SA, Hodge CW. CaMKII inhibition in the prefrontal cortex specifically increases the positive reinforcing effects of sweetened alcohol in C57BL/6J mice. Behav Brain Res. 2016 Feb 1;298(Pt B):286-90. PubMed PMID: 26608538; PubMed Central PMCID: PMC4688209.
4. Cannady R, Fisher KR, Durant B, Besheer J, Hodge CW. Enhanced AMPA receptor activity increases operant alcohol self-administration and cue-induced reinstatement. Addict Biol. 2013 Jan;18(1):54-65. PubMed PMID: 23126443; PubMed Central PMCID: PMC3535558.

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http://www.ncbi.nlm.nih.gov/sites/myncbi/clyde.hodge.1/bibliography/40789261/public/?sort=date&direction=descending