OMB No. 0925-0001 and 0925-0002 (Rev. 03/2020 Approved Through 02-28-2023)

BIOGRAPHICAL SKETCH

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NAME: Morrow, A. Leslie

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

POSITION TITLE: John Andrews Distinguished Professor 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 California, Davis	B.S.	12/1977	Psychobiology
University of California, San Diego	Ph.D.	05/1985	Neuroscience
National Institute of Mental Health	Postdoctoral	06/1988	Molecular Neuropharm.

A. Personal Statement

My work is focused on developing an understanding of the role of $GABA_A$ receptors and neuroactive steroids in normal brain function and neuropsychiatric disease, particularly alcohol use disorders. My group has made landmark discoveries on the role of both $GABA_A$ receptors and neuroactive steroids in ethanol action, ethanol sensitivity, tolerance, dependence and neuroimmune signaling. With regard to this application, we contributed evidence that alterations in $GABA_A$ receptor gene expression and receptor trafficking mediate ethanol dependence symptoms and identified multiple molecular and physiological mechanisms that underlie these adaptations. More recently, we have elucidated epigenetic mechanisms of $GABA_A$ receptor regulation linked to ethanol dependence symptomatology. We further demonstrated how these and other molecular adaptations lead to alterations in the electrophysiological properties of neurons and circuit function within the medial prefrontal cortex (mPFC) and between the mPFC and its target areas, particularly the central nucleus of the amygdala. I am very excited to continue this work with Dr. Melissa Herman in our UNC-ARC component, where we identified sex and cell specific adaptations in mPFC and CeA circuits and mPFC projection neurons that appear to be linked to sex differences in anxiety-like behavior associated with ethanol withdrawal. Our studies will extend this work to address key questions in the field and establish if the neurosteroid allopregnanolone mitigates pathologic ethanol adaptations in rats. As Co-Program Director, I begin my 24th year participating in the leadership of the UNC ARC where I have served many roles over the years and contributed to the evolution of a great team of investigators who lead our field. I am exceedingly optimistic about the translational potential of our basic research and hope to facilitate the continuation of outstanding work through innovation, collaboration and state of the art resources at UNC.

B. Positions and Honors

Positions and Employment

2010-pres: Distinguished Professor, Depts. of Psychiatry and Pharmacology and Center for Alcohol Studies, UNC-CH
2001-pres: Professor, Depts. of Psychiatry and Pharmacology and Center for Alcohol Studies, UNC-CH
1998-pres: Associate Director, Bowles Center for Alcohol Studies, UNC-CH
1996-2001: Associate Professor, Depts. of Psychiatry & Pharmacology and Center for Alcohol Studies, UNC-CH

1990-1996: Assistant Professor, Dept. of Psychiatry and Bowles Center for Alcohol Studies, School of Medicine, University of North Carolina at Chapel Hill (UNC-CH), Chapel Hill, NC
1988-1990: Senior Research Associate, Laboratory of Molecular Pharmacology, NIMH, Bethesda, MD

Other Experience and Professional Memberships

2019 - Review Editor, Scientific Reports
2010 - Principal Editor, Psychopharmacology
2004 - Review Editor, Alcoholism: Clinical and Experimental Research
1990 - Member, Research Society on Alcoholism
1980 - Member, AAAS
1980 - Member, Society for Neuroscience

2009 - 19 Associate Editor, Frontiers in Neuropharmacology
2010 - 17 Associate Editor, Pharmacological Reviews
2010 - 15 Associate Editor, Journal of Pharmacology and Experimental Therapeutics
2007 – 2011 Alcohol Biomedical Research Review Committee, ZAA-4 DD, NIAAA, NIH
2001 – 2003 Chairperson, Biochemistry, Physiology and Medicine Study Section, NIH, NIAAA
1997 – 2001 Biochemistry, Physiology and Medicine Study Section, NIH, NIAAA

Honors

2017 American College of Neuropsychopharmacology Fellow
2015 Bowles Lectureship Award
2010 Johns Andrews Distinguished Professor
2006 APA Frontier of Science Lecturer, APA Annual Meeting, Toronto, Canada, May 24, 2006
2005 NIAAA, NIH R37 Merit Award
1995 University of North Carolina at Chapel Hill Faculty Development Award
1992 Pharmaceutical Manufacturers Research Starter Award
1989 American College of Neuropsychopharmacology Travel Award: Annual Meeting
1988 National Academy of Sciences, National Research Council Associate Award
1986 Pharmacology Research Associate Fellowship (PRAT Fellow). NIGMS, NIH
1983 NIMH Predoctoral Individual Fellowship MH08898.

C. Contributions to Science

1. **Ethanol regulation of $GABA_A$ receptor function, expression and neurotransmission**: My group has shown that ethanol dependence symptoms of anxiety and seizure susceptibility are associated with the loss of GABAergic inhibition in brain. We found ethanol regulation of various $GABA_A$ receptors at the levels of transcription, protein expression, and receptor trafficking. We further established the intracellular signaling mechanisms that underlie ethanol effects on several $GABA_A$ receptor subtypes, including mechanistic roles for PKCγ, PKA and histone acetylation. We are currently expanding these studies to elucidate the ethanol adaptations in circuit mechanisms within the medial prefrontal cortex as well as its projection sites. These studies establish various targets to moderate ethanol withdrawal that could be used for therapeutics.

    a. Bohnsack J.P., Hughes, B.A., O'Buckley, T.K., Edokpolar, K., Besheer, J.B. and **Morrow, A.L**. Histone deacetylases mediate $GABA_A$ receptor expression, physiology, and behavioral maladaptations in rat models of alcohol dependence. Neuropsychopharmacology (2018) 43(7):1518-1529. PMCID:PMC5983537

    b. Hughes, B.A., Bohnsack J.P., O'Buckley, T.K., Herman, M.A. and **Morrow, A.L**. Chronic Ethanol Exposure and Withdrawal Impairs Synaptic $GABA_A$ Receptor-Mediated Neurotransmission in Deep Layer Prefrontal Cortex. Alcohol. Clin. Exp. Res. (2019) 43(5):822-832. PMCID: PMC6502689

c. Hughes, B.A., Crofton, E.J., O'Buckley, T.K., Herman, M.A. and **Morrow, A.L**. Chronic Ethanol Exposure Alters Prelimbic Prefrontal Cortical Fast-Spiking and Martinotti Interneuron Function with Differential Sex Specificity in Rat Brain (2020) Neuropharmacology Jan 1;162:107805. Epub 2019 Oct 4. PMCID: PMC7027948.

d. Hughes, B.A., O'Buckley, T.K., Boero, G., Herman, M.A. and **Morrow, A.L**. Sex- and Subtype-Specific Adaptations in Excitatory Signaling Onto Deep-Layer Prelimbic Cortical Pyramidal Neurons After Chronic Alcohol Exposure (2021) Neuropsychopharmacology. doi: 10.1038/s41386-021-01034-1. Online ahead of print.

2. **Role of neuroactive steroids in ethanol sensitivity, tolerance, dependence and neuroimmune activation:** For many years, the mechanisms of ethanol action were elusive, until we discovered that ethanol-induced increases of GABAergic neuroactive steroids in the brain are required for ethanol sensitivity and contribute to other actions, such as tolerance and dependence. My team has elucidated the mechanisms by which ethanol affects adrenal and brain neurosteroid production and established the physiological significance of these effects. Chronic ethanol exposure leads to increased tolerance to the neurosteroid allopregnanolone, but sensitization to its GABAergic effects, coupled with deficits in brain levels of allopregnanolone that may worsen symptoms of ethanol dependence, including anxiety, seizure susceptibility, and excessive drinking. Recently, we discovered a new mechanism of neurosteroid action – inhibition of Toll-like receptors – that are known to promote ethanol pathology by production of neuroimmune signals. Together, these studies establish a rationale for manipulating (i.e., increasing) allopregnanolone levels for treatment of alcohol use disorders.

   a. Cook J.B., Nelli, S. M., Neighbors, M.R., Morrow, D.H., O'Buckley T.K., Maldonado-Devincci, A.M., **Morrow A.L**. Ethanol alters local cellular levels of (3α,5α)-3-hydroxypregnan-20-one (3α,5α-THP) independent of the adrenals in subcortical brain regions. Neuropsychopharmacology 39:1878-87 (2014). PMCID: PMC4059907

   b. Beattie, M.B., Maldonado-Devincci, A.M., Porcu, P., O'Buckley, T.K., Daunais, J., Grant, K.A., **Morrow, A.L.** Voluntary ethanol consumption reduces GABAergic neuroactive steroid (3α,5α)3-hydroxypregnan-20-one (3α,5α-THP) in the amygdala of the cynomolgus monkey. Addiction Biology (2017) 22(2):318-330. PMCID: PMC4896863

   c. Balan, I., Beattie, M.B., O'Buckley, T.K., Aurelian, L., **Morrow, A.L.** Endogenous Neurosteroid (3α, 5α)3-Hydroxypregnan-20-one Inhibits Toll-like-4 Receptor Activation and Pro-inflammatory Signaling in Macrophages and Brain. Sci Rep. 2019 Feb 4;9(1):1220. DOI: 10.1038/S41598-018-37409-6.

   d. Balan, I., Aurelian, L., Schleicher, R., Boero, G., O'Buckley, T.K., and **Morrow, A.L.** Neurosteroid allopregnanolone (3α,5α-THP) inhibits inflammatory signals induced by activated MyD88-dependent Toll-like receptors (2021) Translational Psychiatry 11:145 -156. https://doi.org/10.1038/s41398-021-01266-1

3. **GABAergic neuroactive steroids are important modulators in animal models of alcohol use disorders:** GABAergic neuroactive steroids mimic many ethanol actions and ameliorate many symptoms of ethanol withdrawal. We thus explored the effects of these steroids on ethanol reinforcement and consumption. Various neuroactive steroids reduce ethanol intake, particularly in dependent rats, but we also found evidence for reductions in ethanol reinforcement after administration of GABAergic neuroactive steroids and precursors. My team further demonstrated that genetic variation in brain levels of the steroids inversely relates to ethanol consumption and place preference. Recently, we used viral-mediated gene delivery to enhance steroidogenesis in ventral tegmental area neurons and demonstrated long-term reductions in ethanol reinforcement and intake. These studies further substantiate the therapeutic potential for these steroids in alcohol use disorders.

   a. Besheer, J., Lindsay, T.G., O'Buckley, T.K., Hodge, C.W., **Morrow, A.L**. Pregnenolone and ganaxolone reduce operant ethanol self-administration in alcohol-preferring P rats. Alcoholism, Clin. Exp. Research. 34(12): 2044-2052 (2010). PMCID: PMC2988984

   b. Porcu, P., **Morrow, A.L**. Divergent neuroactive steroid responses to stress and ethanol in rat and

mouse strains: relevance for human studies. Psychopharmacology (Berl). 231:3257-72 (2014). PMCID: PMC4135033

c. Cook J.B., Werner, D.F., Maldonado-Devincci, A.M., Leonard, M.N., Fisher, K.R., O'Buckley T.K., Porcu, P. McCown, T.J., Besheer, J., Hodge, C.W., **Morrow A.L**. Overexpression of the steroidogenic enzyme cytochrome P450 side chain cleavage in the ventral tegmental area increases 3α,5α-THP and reduces long-term operant ethanol self-administration. J. Neuroscience 34: 5824-5834 (2014). PMCID: PMC3996211

d. Porcu, P., O'Buckley, T.K., Lopez, M.F., Becker, H.C., Miles, M.F., Williams, R.W., **Morrow, A.L.** Initial genetic dissection of serum neuroactive steroids following chronic intermittent ethanol across BXD mouse strains. Alcohol (2017) 58:107-25. PMCID: PMC5253318

4. **Dysregulation of neuroactive steroids in premenstrual dysphoric disorder (PMDD), depression, and schizophrenia:** I have been fortunate to collaborate with leaders in studies of the etiology of these diseases and established that neuroactive steroids contribute to their pathophysiology. My team used radioimmunoassays and ELISAs to measure allopregnanolone and developed the only GCMS assay to measure all eight GABAergic neuroactive steroids – specifically in human serum. Our studies show that allopregnanolone is elevated in patients with PMDD and this elevation blunts stress responses, including the stress-induced elevation of allopregnanolone. Subjects with a history of depression have reduced levels of all pregnane neuroactive steroids and blunted responses to progesterone challenge. Progesterone and allopregnanolone levels are inversely related to mood, sleep and emotional disturbances in second trimester pregnant women. Pregnenolone supplementation has therapeutic benefits in patients with schizophrenia. These studies suggest that deficits in neuroactive steroids promote risk and pathophysiology of various neuropsychiatric diseases.

   a. Porcu, P., O'Buckley, T.K., Alward, S.E., Marx, C.E., Shampine, L.J., Girdler, S.S., **Morrow, A.L**. Simultaneous quantification of GABAergic 3α,5α and 3α,5β neuroactive derivatives of pregnenolone in human and rat serum. Steroids 74:463-73 (2009). PMCID: PMC2832187

   b. Girdler, S.S., Lindgren, M., Porcu, P., Rubinow, D.R., Johnson, J.L., **Morrow, A.L**. A History of depression in women is associated with an altered GABAergic neuroactive steroid profile. Psychoneuroendocrinology 37:543-53 (2012) PMCID: PMC3233657

   c. Boero, G., Porcu, P., **Morrow, A.L.** Pleiotropic Actions of Allopregnanolone Underlie Therapeutic Benefits in Stress-Related Disease. Neurobiology of Stress (2019) NOV 27;12:100203. DOI: 10.1016/J.YNSTR.2019.100203. PMID:31879693 Free Article

   d. Boero, G., Tyler, R.E., Todd, C.A., O'Buckley, T.K., Balan, I., Besheer, J., and **Morrow, A.L.** (3α,5α)3-Hydroxypregnan-20-one (3α,5α-THP) regulation of hypothalamic and extrahypothalamic corticotropin releasing factor (CRF): Sexual dimorphism and brain region specificity in Sprague Dawley rats (2021) Neuropharmacology. Mar 15;186:108463. doi: 10.1016/j.neuropharm.2021.108463. PMCID: PMC8010646

Complete List of Published Work in MyBibliography:

http://www.ncbi.nlm.nih.gov/sites/myncbi/a.leslie.morrow.1/bibliography/48146177/public/?sort=date&direction=ascending

D. Research Support - Ongoing Research Support

5 P60 AA11605 Kash/Morrow - Co-PDs 12/01/2017 - 11/30/2022
NIH/NIAAA
Molecular and Circuit Pathogenesis in Alcoholism
The major goals of this project are to determine molecular and circuit pathogenesis of alcohol addiction.
Role: Co-PD

5 P60 AA11605 Kash/Morrow - Co-PDs 12/01/2017 - 11/30/2022
NIH/NIAAA

Molecular and Circuit Pathogenesis in Alcoholism - Research Component 4 –
GABAergic Corticolimbic Circuit Mechanisms of Ethanol Dependence - Morrow/Herman (co-PIs)
This component will examine the overall hypothesis that chronic ethanol exposure alters local mPFC and amygdalar microcircuits as well as the mPFC projection to central amygdala in conjunction with $GABA_A$ receptor adaptations that can be prevented by histone acetylation.
Role: Research Component Co-PI

R01 AA024095 Morrow - PI 05/01/2017 - 03/31/2022
NIH/NIAAA
Gene Delivery of Neuroactive Steroids to Modulate Ethanol Reinforcement/Consumption
The goal of this project is to evaluate the hypotheses that elevated steroidogenesis in the ventral tegmental area will reduce operant ethanol self-administration and the escalation of voluntary drinking.
Role: PI

Foundation of Hope Morrow, PI 7/1/20 – 6/30/22
Foundation of Hope
Mechanisms of Brexanolone® Therapeutics in Post-Partum Depression
This project will determine if Brexanolone therapy for Post-Partum Depression inhibits inflammatory signals or enhances anti-inflammatory signals in patient serum in a manner that correlates with treatment response.

Sponsored Research Agreement II Morrow - PI 2/1/21 – 1/31/23
Sage Therapeutics
Allopregnanolone and THDOC Enhancement of Anti-Inflammatory Signals
The goal of this project is to evaluate the mechanisms of endogenous neurosteroid enhancement of ANTI-INFLAMMATORY Fracktalkine and IL-10 signaling in monocytes/macrophages and the brain.
Role: PI

1K01 DA046561 Milivojevic - PI 02/01/18 - 01/30/24
NIH/NIDA
Neuroactive steroids in stress, drug craving and drug use in cocaine use disorders
This project will examine the role of varying doses of the neuroactive steroid precursor pregnenolone on drug craving, stress arousal and clinical cocaine use outcomes in individuals with cocaine use disorders.
The purpose of this award is to facilitate the career development of Dr. Milivojevic.
Role: Co-mentor, Consultant

<u>Completed Research Support</u>

Sponsored Research Agreement I Morrow - PI 07/09/2019 - 07/08/2021
Sage Therapeutics
Mechanism(s) of neurosteroid-mediated inhibition of TLR signaling
The goal of this project is to test the effects of neuroactive steroids on TLR signaling in cultured human macrophages and alcohol-preferring (P) rat brain and to determine the mechanisms of inhibition.
Role: PI

R01DA037289 Subcontract Morrow - PI 12/01/2017 - 11/30/2019
NIH/NIDA
Neuroactive steroids in nicotine addiction: Effects of progesterone challenge
The purpose of this subcontract was to determine both baseline and progesterone-induced levels of eight GABAergic neuroactive steroids in male and female human subjects with current nicotine addiction.
Role: PI