BIOGRAPHICAL SKETCH

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NAME: Melissa A. Herman

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

POSITION TITLE: Assistant Professor

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
Boston University, Boston MA	B.S.	06/2001	Human physiology
Georgetown University, Washington DC	Ph.D.	06/2010	Neuroscience
The Scripps Research Institute, La Jolla CA	Post-doc	08/2015	Neuropharmacology

A. Personal Statement

I am in the process of establishing my laboratory as an Assistant Professor in the Pharmacology Department and the Bowles Alcohol Research Center at the University of North Carolina. I have a broad background in neurophysiology and neuropharmacology, and I have been trained as a multidisciplinary scientist. My research interests involve the structure of inhibitory neuronal networks and how these networks change to produce adverse behavioral outcomes. My main interest is how the inhibitory neurotransmitter gamma-aminobutyric acid (GABA) regulates neuronal networks via both synaptic and extrasynaptic forms of inhibition and how alterations in inhibitory networks contribute to clinical conditions such as alcohol use disorder, nicotine, addiction, or stress. My work has focused primarily on three brain regions: the nucleus tractus solitaries (NTS), central and basolateral amygdala, and ventral tegmental area. In each of these areas I have identified local inhibitory networks that control overall excitability and that are dysregulated by exposure to acute and or chronic exposure to alcohol or nicotine.

B. Positions and Honors

Positions

1997-2001 **Boston University** (Boston, MA) – Sargent College of Health and Rehabilitation Studies
Undergraduate student

2001-2005 **The Salk Institute for Biological Studies** (La Jolla, CA) – Department of Peptide Biology
Research assistant
Advisor: Dr. Catherine Rivier

2005-2010 **Georgetown University Medical School** (Washington DC) – Department of Pharmacology
Postdoctoral scholar
Advisor: Richard Gillis

2010-2015 **The Scripps Research Institute** (La Jolla, USA) - Committee on the Neurobiology of Addictive Disorders
Research Associate
Advisor: Dr. Marisa Roberto

2016-present **The University of North Carolina** (Chapel Hill, NC) – Department of Pharmacology, Bowles Center for Alcohol Studies

Assistant Professor

Professional Memberships and Activities

2005-present	Society for Neuroscience
2011-present	Research Society on Alcoholism
2013-2014	FRONTIERS SPECIAL TOPICS JOURNAL EDITOR Co-Editor of "Neurophysiological mechanisms of addictive disorders" Special Topic for *Frontiers in Integrative Neuroscience*

Honors

1998, 2001	Boston University Dean's List
2006-2009	Travel Award Georgetown University Medical Center Graduate Student Organization
2010	Ph.D. distinction award, Georgetown University Medical Center
2011, 2013	Travel Award, NIAAA Special Meeting "Alcoholism and Stress: a Framework for future treatment strategies" Volterra, Italy
2011-2014	Post-doctoral fellowship from NIAAA
2013	Poster award NIAAA Special Meeting "Alcoholism and Stress: a Framework for future treatment strategies" Volterra, Italy

C. Contribution to Science

1. The role of the autonomic nervous system in the central control of gastric function is well known, however, the specific signaling and circuitry mediating this control remain poorly understood. My early work focused on the role of inhibitory signaling in the brainstem nucleus the Nucleus Tractus Solitarius (NTS) and the role of inhibition in the central control of gastric function. My work revealed an important role for inhibitory signaling in the NTS in the control of basal gastric function. I also reported on a novel form of inhibition in the NTS, tonic or extrasynaptic inhibition, and showed how tonic inhibition acted as a critical regulator of overall network activity in the NTS. In addition, I showed how stimulation of the mu-opioid receptor in the NTS altered inhibitory function by dampening tonic inhibition resulting in diminished gastric tone. Collectively this work demonstrates the importance of inhibitory control in maintaining physiological gastric function and provides a central mechanism by which opioid therapeutics can produce adverse gastric side effects.

   a) Herman MA, Cruz MT, Sahibzada N, Verbalis JG, Gillis RA. GABA signaling in the Nucleus Tractus Solitarius sets the level of activity in Dorsal Motor Nucleus of the Vagus cholinergic neurons in the vago-vagal circuit. Am J Physiol Gastrointest Liver Physiol. 2009 Jan;296(1):G101-11.

   b) Herman MA, Alayan A, Sahibzada N, Bayer B, Verbalis JG, Dretchen K, Gillis RA. Mu-opioid receptor stimulation in the medial subnucleus of the tractus solitarius (mNTS) inhibits gastric tone and motility by reducing local GABA activity. Am J Physiol Gastrointest Liver Physiol. 2010 Aug;299(2):G494-506.

   c) Herman MA, Gillis RA, Vicini S, Dretchen K, Sahibzada N. Tonic GABAA receptor conductance in medial subnucleus of the tractus solitarius (mNTS) neurons is inhibited by activation of μ-opioid receptors. J Neurophysiol. 2012 Feb;107(3):1022-31.

2. The central nucleus of the amygdala (CeA) is a key brain region in the negative reinforcing properties of ethanol and has been implicated in both the development of alcohol dependence as well as the susceptibility to relapse in dependent individuals. Inhibitory signaling in the CeA has been shown to play a major role in both the effects of acute ethanol as well as the neuroadaptations that occur in response to chronic ethanol exposure. Until recently, the majority of the work done has been focused on phasic or synaptic inhibition and has treated the CeA as a homogenous nucleus, with little investigation into cell type-specific effects. In my work I utilized a transgenic reporter mouse expressing green fluorescent protein (GFP) under the control of the CRF receptor 1 promoter to identify CRF1-

expressing (GFP+) neurons in the CeA. Using these mice as well as a rat model, I uncovered cell type-specific expression of tonic inhibitory signaling in CeA neurons with differential sensitivity to the effects of by acute ethanol. I also identified a local inhibitory microcircuit within the CeA which provides the local synaptic mechanism for the divergent effects of acute ethanol on the firing of distinct CeA neurons. The types of tonic inhibition in the CeA are selectively altered by exposure to chronic intermittent ethanol, with significant consequences for overall ceA network function. In addition, work in mice containing a genetic deletion of the interleukin receptor 1 receptor antagonist revealed that tonic inhibition was selectively altered in CeA neurons in a manner similar to what was observed following chronic ethanol exposure. This work highlights the significance of tonic inhibition in the physiological functioning of the CeA and adds tonic signaling to the neuroadaptations that occur with chronic alcohol exposure and further suggests that alterations in tonic signaling is implicated in other pathophysiological conditions like inflammation and/or stress.

a) Herman MA, Contet C, Justice NJ, Vale W & Roberto M. Novel subunit-specific tonic GABA currents and differential effects of ethanol in the central amygdala of CRF receptor-1 reporter mice. *J Neurosci* 2013, 33(8):3284-98. PMC3711798.

b) Herman MA and Roberto M. Cell type-specific tonic GABA signaling in the rat central amygdala is selectively altered by acute and chronic ethanol. Addiction Biology. 2014 Aug 29. [Epub ahead of print]

c) Bajo M, **Herman MA**, Varodayan FP, Oleata CS, Madamba SG, Harris RA, Blednov YA, Roberto M. Role of the IL-1 receptor antagonist in ethanol-induced regulation of GABAergic transmission in the central amygdala. Brain Behavior and Immunity. 2014 Dec 3. [Epub ahead of print]

G protein-gated inwardly-rectifying potassium (GIRK) channels and large conductance, calcium- and voltage-activated potassium (BK) channels. Despite *in vitro* evidence that ethanol can bind and activate these channels, whether these actions contribute to the behavioral effects of ethanol remains largely unknown. We have addressed this question by characterizing knockout mice missing GIRK or BK channel subunits. In particular, we have shown that GIRK3 gates activation of the mesolimbic dopaminergic system by ethanol, with direct consequences on binge-like drinking.

3. The ventral tegmental area (VTA) is a major component of the mesolimbic dopamine reward pathway. Changes in the activity of dopamine neurons in the VTA is associated with increased (or decreased) dopamine release in target brain regions like the nucleus accumbens and this signaling is thought to provide one aspect of the cellular basis for reward signaling. Accordingly, certain drugs of abuse are known to selectively engage dopamine neurons in the VTA and this signaling is thought to contribute to the development of addiction. Despite the importance of changes in the excitability of VTA dopamine neurons in normal reward processing as well dysregulation of this signaling in pathological conditions such as addiction and psychiatric disorders like depression, the cellular mechanisms controlling the firing of dopamine neurons are poorly understood. My work has examined inhibitory and excitatory regulation of dopamine neurons in the VTA. Specifically I have shown that activation of the dopamine D2 receptor and the CRF receptor increases excitatory signaling at VTA dopamine neurons. I have also shown that inhibitory control of VTA dopamine neurons is compromised by chronic exposure to nicotine in a mechanism involving the CRF system and that the excitatory actions of ethanol in VTA dopamine neurons is mediated at least in part by the G protein-gated inwardly-rectifying potassium (GIRK) 3 subunit channel.

a) Nimitvilai S, **Herman** M, You C, Arora DS, McElvain MA, Roberto M, Brodie MS. Dopamine D2 receptor desensitization by dopamine or corticotropin releasing factor in ventral tegmental area neurons is associated with increased glutamate release. Neuropharmacology. 2014 Jul;82:28-40.

b) Grieder TE, **Herman M**, Contet C, Tan LA, Vargas-Perez H, Cohen A, Chwalek M, Maal-Bared G, Freiling J, Schlosburg JE, Clarke L, Crawford E, Koebel P, Canonigo V, Sanna P, Tapper A, Roberto M, Kieffer BL, Sawchecko PE, Koob GF, van der Kooy D & George O. CRF neurons in the

ventral tegmental area control the aversive effects of nicotine withdrawal and promote escalation of nicotine intake. *Nature Neurosci* 2014, 17(12):1751-8. PMC4241147.

c) Herman MA, Munoz MB, Le D, Kreifeldt M, Stouffer DG, Parsons LH, Roberto M, Roberts AJ, Wickman K, Slesinger PA and Contet C. GIRK3 gates activation of the mesolimbic dopaminergic pathway by ethanol. Proc Natl Acad Sci. 2015 Jun 2;112(22):7091-6.

Complete List of Published Work in MyBibliography:
http://www.ncbi.nlm.nih.gov/sites/myncbi/melissa.herman.1/bibliography/43552900/public/?sort=date&direction=descending

D. Research Support

Ongoing Research Support

NIAAA K99AA023002 8/2015-9/2020

"Alcohol-induced plasticity within CRF1 microcircuits in distinct amygdala nuclei"

Role: PI

Completed Research Support

NIAAA F32 AA020430 8/2011-9/2014

"Tonic GABAA receptor signaling in the Central Amygdala and alcohol dependence"

Role: PI

T32DA007291 9/2007-6/2009

National Institute of Drug Abuse (NIDA) Training Grant, Georgetown University