BIOGRAPHICAL SKETCH

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NAME: Downs, Anthony

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

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)	END DATE MM/YYYY	FIELD OF STUDY
Warren Wilson College, Swannanoa, North Carolina	BS	12/2012	Biology
Emory University, Atlanta, Georgia	PHD	01/2021	Pharmacology
University of North Carolina at chapel Hill, Chapel Hill, North Carolina	Postdoctoral Fellow	10/2023	Neuropharmacology

A. Personal Statement

My prior and ongoing education and research training have given me a broad background in pharmacology, neurochemistry, ex vivo slice recordings, and mouse genetics. As a research technician in the lab of Dr. Donald Hoover, I conducted research on the development and plasticity of the cardiac nervous system and neuro-immune interactions during sepsis. For my doctoral training in the lab of Dr. Ellen Hess, I studied mechanisms leading to reduced dopamine neurotransmission in a genetic mouse model of dystonia and uncovered a potential mechanism of action by which muscarinic receptor antagonists can normalize striatal dopamine neurotransmission in this model. During my time in Dr. Hess's lab **I was awarded an NRSA F31 fellowship** and published three first author papers. I joined Dr. McElligott' s lab for my postdoctoral training to study neurophysiological changes in central noradrenergic signaling that underlie neuropsychiatric disorders. During this time, **I trained under the BCAS postdoctoral T32**, and I have used ex vivo slice electrophysiology to examine the effects of tauopathy and alcohol consumption on locus coeruleus physiology. This proposed research project will examine alterations in central noradrenergic signaling in the context of opioid use disorder. **This project will provide new technical training in transcriptomics and bioinformatic approaches to uncover changes in plasticity of select neuronal populations. It will also provide further training in mouse behavioral paradigms of fear and stress and *in vivo* fiber photometry**. This project provides career development opportunities for conference attendance, networking, and lab management to facilitate my transition from a mentored trainee to an independent scientist.

B. Positions, Scientific Appointments and Honors

Positions and Scientific Appointments

2023 - Assistant Professor, University of North Carolina at Chapel Hill, Chapel Hill, NC
2021 - 2023 Postdoctoral Research Fellow, University of North Carolina at Chapel Hill, Chapel Hill, NC
2015 - 2021 Graduate Student Researcher, Emory University, Atlanta, GA
2013 - 2015 Research Technician, East Tennessee State University, Johnson City, TN

Other Experience and Professional Memberships

Manuscript Review: *Neurobiology of Disease, Journal of Pharmacology and Experimental Therapeutics, Neurobiology of Stress*

Honors

2017 - 2021 Predoctoral Individual National Research Service Award, NIH-NINDS

2016 - 2017 Pharmacological Sciences Training Grant, NIH-General Medical Sciences
2021 – 2023 Alcohol Studies Postdoctoral Training Grant, NIH-NIAAA

C. Contribution to Science

1. During my doctoral training, I studied defects in striatal dopamine neurotransmission in mouse models of dystonia. Mouse models of DYT1-TOR1A dystonia have significant reductions in striatal dopamine neurotransmission. While we did not find the precise mechanism for this reduction, we did find that the deficit in Dopamine release is due to the direct effects of the mutant TOR1A gene on midbrain dopamine neurons. Using a mouse model of DOPA-responsive dystonia, we uncovered changes in ERK signaling in both direct and indirect striatal projection neurons that underlie dystonia in this model.

    a. Roman KM, Briscione MA, Donsante Y, Ingram J, Fan X, Bernhard D, Campbell SA, Downs AM, Gutman D, Sardar TA, Bonno SQ, Sutcliffe DJ, Jinnah HA, Hess EJ. Striatal Subregion-selective Dysregulated Dopamine Receptor-mediated Intracellular Signaling in a Model of DOPA-responsive Dystonia. Neuroscience. 2023 May 1;517:37-49. PubMed Central PMCID: PMC10085842.
    b. Briscione MA, Dinasarapu AR, Bagchi P, Donsante Y, Roman KM, Downs AM, Fan X, Hoehner J, Jinnah HA, Hess EJ. Differential expression of striatal proteins in a mouse model of DOPA-responsive dystonia reveals shared mechanisms among dystonic disorders. Mol Genet Metab. 2021 Aug;133(4):352-361. PubMed Central PMCID: PMC8292208.
    c. Downs AM, Fan X, Kadakia RF, Donsante Y, Jinnah HA, Hess EJ. Cell-intrinsic effects of TorsinA(ΔE) disrupt dopamine release in a mouse model of TOR1A dystonia. Neurobiol Dis. 2021 Jul;155:105369. PubMed Central PMCID: PMC8327367.

2. One of the main therapeutics used to treat dystonia are muscarinic receptor antagonists. While these agents are effective, they are often poorly tolerated due to significant side effects. I investigated which muscarinic receptor subtypes mediate potential therapeutic mechanisms in a mouse model of DYT1-TOR1A dystonia, in the hope that this would lead to more specific therapeutics. I found that the non-selective muscarinic receptor antagonist normalizes striatal dopamine release in a mouse model of DYT1-TOR1A dystonia. Using a combination of newly developed subtype-specific muscarinic receptor antagonists and cell-type specific muscarinic receptor knockout mice, I determined that this dopamine enchanting effect was due to blockade of M4 muscarinic receptors on striatal cholinergic interneurons.

    a. Downs AM, Donsante Y, Jinnah HA, Hess EJ. Blockade of M4 muscarinic receptors on striatal cholinergic interneurons normalizes striatal dopamine release in a mouse model of TOR1A dystonia. Neurobiol Dis. 2022 Jun 15;168:105699. PubMed PMID: 35314320.
    b. Downs AM, Roman KM, Campbell SA, Pisani A, Hess EJ, Bonsi P. The neurobiological basis for novel experimental therapeutics in dystonia. Neurobiol Dis. 2019 Oct;130:104526. PubMed Central PMCID: PMC6885011.
    c. Downs AM, Fan X, Donsante C, Jinnah HA, Hess EJ. Trihexyphenidyl rescues the deficit in dopamine neurotransmission in a mouse model of DYT1 dystonia. Neurobiol Dis. 2019 May;125:115-122. PubMed Central PMCID: PMC6863078.

3. Epidemiological data suggests a link between life-long alcohol consumption and the later development of tauopathy disorders, including Alzheimer's disease and frontotemporal dementia. However, relatively little is known about interactions between alcohol and tauopathy in specific neuronal circuits. We investigated the effects of long-term intermittent access to alcohol on locus coeruleus function in the P301S mouse model of tauopathy. We found significant changes to excitatory inputs to the LC following alcohol consumption, but this effect was absent in P301S mice. Alcohol consumption also enhanced excitability of locus coeruleus neurons, and this effect was enhanced in female P301S. Together this work demonstrates complex interactions between alcohol consumption, tau status, and sex on locus coeruleus function.

    a. Downs AM, Catavero CM, Kasten MR, McElligott ZA. Tauopathy and alcohol consumption interact to alter locus coeruleus excitatory transmission and excitability in male and female mice. Alcohol. 2023 Mar;107:97-107. PubMed PMID: 36150608.

4. Central noradrenergic signaling is known to play a significant role in multiple types of substance use disorder. Noradrenergic signaling modifies the rewarding properties of drugs, stress-induced reinstatement of drug seeking, and withdrawal states. Notably, drugs that reduce noradrenergic transmission are used clinically to reduce alcohol cravings and reduce the symptoms of both alcohol and opioid withdrawal. We hope to uncover changes in plasticity of noradrenergic neurons in the nucleus of the solitary tract. as this population has been implicated in both the rewarding properties and withdrawal symptoms of opioids. This could aid in the development of better therapeutics for opioid withdrawal.

    a. Downs AM, McElligott ZA. Noradrenergic circuits and signaling in substance use disorders. Neuropharmacology. 2022 May 1;208:108997. PubMed Central PMCID: PMC9498225.

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