BIOGRAPHICAL SKETCH

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NAME: Thomas Louis Kash

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

POSITION TITLE: John Andrews Distinguished Professor, Center Director

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
SUNY College of Environmental Science	BS	1999	Chemistry
Weill Cornell Graduate School of Medical Sciences	PhD	2004	Neuroscience
Vanderbilt University Medical Center	Post-Doc	2008	Molecular Physiology

A. Personal Statement

I am a Professor in Pharmacology and the director of the Bowles Center for Alcohol Studies. I am currently PI or co-PI on multiple research grants, including Component 5 and admin core of the NIAAA-funded UNC P60 Alcohol Research Center as well as a U01 that I am MPI with Dr. McElligott. My broad scientific goal is to understand how modulation of discrete neuronal circuits can shape behavior and to deconstruct the molecular mechanisms that underlie this modulation. Research in my lab is focused on understanding how stress, pain and alcohol abuse can alter neuronal function in brain regions that regulate emotional behavior. These topics are fascinating from a basic science standpoint, but also absolutely critical from the public health standpoint, as these disorders exert a tremendous economic impact on our society. These investigations are performed using a multidisciplinary approach, ranging from behavioral analysis to detailed mechanistic signaling analysis in individual neurons. My long-term goal is to integrate our studies using translational and reverse translational approaches to identify novel treatments and biomarkers for psychiatric disorders.

Grants - Active

R01NS122230 (PI: Kash) 04/15/2021 – 3/31/2026
NIH/NINDS: Determining the impact of BNST CRF systems on inflammatory pain-induced disruptions of behavior

R01AA019454 (PI: Kash) 08/05/2010 – 01/31/2029
NIH/NIAAA: Extended Amygdala Regulation of Dorsal Raphe Function in Ethanol Self-Administration

Role: PIR01AA022048 (PI: Thiele, Kash) 04/01/2022 – 3/31/2027
NIH/NIAAA: *The Role of CRF in Binge-Like Ethanol Drinking*

U01 AA020911 (PI: McElligott, Kash) 02/10/2012 – 1/31/2027
NIH/NIAAA: 5/8 INIA Stress and Chronic Alcohol Interactions: Probing brain circuits that regulate alcohol stress interactions

5P60AA011605 (Kash) 12/01/2012 – 11/20/2027
NIH/NIAAA: Molecular and Cellular Pathogenesis in Alcoholism
Role: Co-PI of Component 5

5P60AA011605 (Kash) 12/01/2012 – 11/20/2027
NIH/NIAAA: Molecular and Cellular Pathogenesis in Alcoholism

T32GM152779 (PI: Robinson, Kash, Crews) 04/01/1997 –03/31/2028
NIH/NIAAA: Molecular and Cellular Alcohol Research Training

B. Positions, Scientific Appointments, and Honors

Positions

2023 -	Director, Bowles Center for Alcohol Studies
2019-	Professor, Department of Pharmacology
2017 - 2023	Vice Chair of Faculty Development, Department of Pharmacology
2015 – 2019	Associate Professor, Department of Pharmacology
2009 - 2015	Assistant Professor, Department of Pharmacology
2008 - 2009	Research Instructor, Department of Molecular Physiology and Biophysics, Vanderbilt University
2004 - 2008	Post-doctoral Research Fellow, Mentor: Danny G. Winder, Ph.D. Department of Molecular Physiology and Biophysics ,Vanderbilt University
2000 - 2004	Ph.D. in Neuroscience, Mentor: Neil L. Harrison, Ph.D. Weill Graduate College of Biomedical Science, Cornell University

Honors

2023	Amygdala GRC Chair
2019	Jacob Waletzky Award
2019	Amygdala GRC Vice Chair
2018	ACNP Member
2014	NARSAD Independent Investigator Award
2014	ACNP Associate Member
2013	Research Society for Alcoholism Young Investigator Award
2011	White House Presidential Early Career Award for Scientists and Engineers

Other Experience and Professional Memberships

2023-	Brain and Behavior Research Foundation Scientific Council Member
2023-	NIDA BSC member
2018	Ad Hoc NIH Peer Review, NAL
2015-	Editorial Board: Journal of Neuroscience, Molecular Pharmacology, Neuropharmacology, Molecular Neuropsychopharmacology
2014-2017	NIH Peer Review, MNPS Member
2011-13	NIH Peer Review Committee: MNPS Ad hoc
2006-	Member, Research Society for Alcoholism
2001-	Member, Society for Neuroscience

C. Contributions to Science

1. **ALCOHOL/STRESS REGULATION OF 5HT SYSTEMS** As I began my lab, I developed an interest in 5-HT. This stemmed from a number of interesting clinical pharmacology papers from the Kranzler, Krystal and Heilig groups. Moreover, given the rich pharmacology of 5HT, I thought it was something that may develop traction translationally. In the initial stage of this exploration, the lab did more basic work trying to understand how alcohol exposure modulated synaptic function across the brain. We then directly targeted

5HT signaling in the bed nucleus of the stria terminalis (BNST) following chronic intermittent alcohol exposure, looking at both electrophysiological adaptations, markers of activity and relating this to behavior. At the same time, we began looking at alcohol's impact in the dorsal raphe (DR), and found some interesting effects with chronic alcohol altering function, and response to acute alcohol, suggesting that this is a potential site of negative reinforcement. From here, we began to focus on more mechanistic circuit based work, trying to understand Gq signaling in the BNST and 5HT modulation of function. We recently performed a deep mechanistic analysis of 5HT2C activity in the BNST and Lateral Habenula, as they relate to alcohol consumption and withdrawal driven behavioral deficits. Current efforts are focused on understanding how 5HT signaling can drive excessive alcohol consumption via actions of CRF in the DR.

a. Pleil KE, Lowery-Gionta EG, Crowley NA, Li C, Marcinkiewcz CA, Rose JH, McCall NM, Maldonado-Devincci AM, Morrow AL, Jones SR, **Kash TL** (2015a) Effects of chronic ethanol exposure on neuronal function in the prefrontal cortex and extended amygdala. Neuropharmacology 99:735-749.

b. Marcinkiewcz CA, Dorrier CE, Lopez AJ, **Kash TL** (2015) Ethanol induced adaptations in 5-HT2c receptor signaling in the bed nucleus of the stria terminalis: implications for anxiety during ethanol withdrawal. Neuropharmacology 89:157-167.

c. Lowery-Gionta EG, Marcinkiewcz CA, **Kash TL** (2015) Functional alterations in the dorsal raphe nucleus following acute and chronic ethanol exposure. Neuropsychopharmacology 40:590-600.

d. Flanigan ME, Hon OJ, D'Ambrosio S, Boyt KM, Hassanein L, Castle M, Haun HL, Pina MM, Kash TL. Subcortical serotonin $5HT_{2c}$ receptor-containing neurons sex-specifically regulate binge-like alcohol consumption, social, and arousal behaviors in mice. Nat Commun. 2023 Mar 31;14(1):1800. doi: 10.1038/s41467-023-36808-2. PMID: 37002196; PMCID: PMC10066391.

2. **DISSECTING CIRCUITS UNDERLYING PATHOLOGICAL BEHAVIORS.** With the advent of optogenetics and chemogenetics, there are now many tools available to probe the role of circuits and cells in given behaviors and modulation. My focus has primarily been on how the extended amygdala can regulate anxiety like behavior, publishing several high impact papers focusing on the role of neuromodulation in the BNST and how that is related to both alcohol and anxiety.

    a. Marcinkiewcz CA*, Mazzone CM*, D'Agostino G, Halladay LR, Hardaway JA, DiBerto JF, Navarro M, Burnham N, Cristiano C, Dorrier CE, Tipton GA, Ramakrishnan C, Kozicz T, Deisseroth K, Thiele TE, McElligott ZA, Heisler LK and **Kash TL.** Serotonin Activates an Anxiety and Fear Promoting Circuit in the BNST. Nature.

    b. Vardy E, Robinson JE, Li C, Olsen R, Crowley NA, Pleil KE, Mazzone CA, **Kash TL,** Krashes M, Roth BL. A New DREADD Facilitates the Multiplexed Chemogenetic Interrogation of Behavior. Neuron.

    c. Li C, Sugam JA, Lowery-Gionta EG, McElligott ZA, McCall NM, Lopez AJ, McKlveen JM, Pleil KE, Kash TL (2016) Mu Opioid Receptor Modulation of Dopamine Neurons in the Periaqueductal Gray/Dorsal Raphe: A Role in Regulation of Pain. Neuropsychopharmacology.

3. **NEUROPEPTIDE MODULATION OF SYNAPTIC FUNCTION AND PLASTICITY.** While a post-doc I also began examining how neuropeptides, in particular CRF and NPY, interact and regulate synaptic function and plasticity. This work was critical as it built on a large body of behavioral data suggesting that these modulators can play critical roles in the regulation of both stress and addiction related behavior. I provided the first evidence of a direct molecular interaction between CRF and NPY, and in addition demonstrated that biogenic amines such as dopamine and norepinephrine can engage peptide signaling in this structure, and these systems are altered by cocaine exposure. More recent work has focused on kappa opioid receptor signaling in the amygdala.

    a. ***Kash TL**, *Nobis WP, Matthews RT and Winder DG. Dopamine enhances fast excitatory synaptic transmission in the extended amygdala by a CRF-R1-dependent process. J Neurosci. 2008;28(51):13856-13865.

b. Nobis WP*, **Kash TL***, Silberman Y and Winder DG. beta-Adrenergic receptors enhance excitatory transmission in the bed nucleus of the stria terminalis through a corticotrophin-releasing factor receptor-dependent and cocaine-regulated mechanism. Biol Psychiatry. 2011;69(11):1083-1090.

c. **Kash TL** and Winder DG. Neuropeptide Y and corticotropin-releasing factor bi-directionally modulate inhibitory synaptic transmission in the bed nucleus of the stria terminalis. Neuropharmacology. 2006;51(5):1013-1022.

d. Bloodgood DW, Hardaway JA, Stanhope CM, Pati D, Pina MM, Neira S, Desai S, Boyt KM, Palmiter RD, **Kash TL**. Kappa opioid receptor and dynorphin signaling in the central amygdala regulates alcohol intake. Mol Psychiatry. 2021 Jun;26(6):2187-2199. doi: 10.1038/s41380-020-0690-z. Epub 2020 Feb 25. PMID: 32099099; PMCID: PMC8124770.

4. **CIRCUIT ANALYSIS OF EXCESSIVE ALCOHOL DRINKING.** After moving to UNC, I started collaborating with Todd Thiele examining how neuropeptides can influence binge-drinking. Together we have published several high impact papers delineating mechanisms by which and adaptations in neuropeptide systems in the extended amygdala. These work were critical to the field because they demonstrated that high level drinking could engage stress systems such as CRF without the animals being alcohol dependent. More recently, we used a whole brain unbiased approach to identify the CoA as a key region for escalated alcohol consumption, the basis of this proposal.

   a. Pleil KE, Lowery-Gionta EG, Rinker JA, McCall NM, Sprow GM, Olson DP, Mazzone CM, Lowell BB, Grant KA, Thiele TE, **Kash TL.** NPY Signaling Inhibits Extended Amygdala CRF Neurons to Suppress Binge Alcohol Drinking. Nature Neuroscience

   b. Lowery-Gionta EG, Navarro M, Li C, Pleil KE, Rinker JA, Cox BR, Sprow GM, **Kash TL** and Thiele TE. Corticotropin releasing factor signaling in the central amygdala is recruited during binge-like ethanol consumption in C57BL/6J mice. J Neurosci. 2012;32(10):3405-3413.

   c. Roland AV, Coelho CAO, Haun HL, Gianessi CA, Lopez MF, D'Ambrosio S, Machinski SN, Kroenke CD, Frankland PW, Becker HC, **Kash TL**. Alcohol Dependence Modifies Brain Networks Activated During Withdrawal and Reaccess: A c-Fos-Based Analysis in Mice. Biol Psychiatry. 2023 Sep 1;94(5):393-404. doi: 10.1016/j.biopsych.2023.01.018. Epub 2023 Feb 1. PMID: 36736419.

5. **ION CHANNEL MOLECULAR ANALYSIS** My initial publications were focused at delineating the structural mechanisms involved in the activation of ligand gated ion channels, with a particular focus on GABAA receptors. This was a critically important topic, as these receptors are targets of many drugs, including anesthetics, ethanol and benzodiapines and are involved in a bevy of brain disorders. At this point in time, the mechanism by which the energy of ligand binding was coupled to channel opening was unknown. Using a combination of site directed mutagenesis, electrophysiology, and molecular modeling, I was the lead on multiple manuscripts describing a molecular interaction within the GABAA receptor that was responsible for the coupling of these processes. These key findings have formed the basis for a greater understanding of ion channel function and the concepts proposed a decade ago have been validated in new crystal structures.

   a. **Kash TL**, Jenkins A, Kelley JC, Trudell JR and Harrison NL. Coupling of agonist binding to channel gating in the GABA(A) receptor. Nature. 2003;421(6920):272-275.

   b. **Kash TL**, Dizon MJ, Trudell JR and Harrison NL. Charged residues in the beta2 subunit involved in GABAA receptor activation. J Biol Chem. 2004;279(6):4887-4893.

   My NCBI Bibliography:

http://www.ncbi.nlm.nih.gov/myncbi/browse/collection/40778790/?sort=date&direction=ascending