BIOGRAPHICAL SKETCH

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NAME: Thomas Louis Kash

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

POSITION TITLE: Associate professor

EDUCATION/TRAINING

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

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 and drug abuse can alter neuronal function in brain regions that regulate emotional behavior. This is a topic that is fascinating from a basic science standpoint, but also absolutely critical from the public health standpoint, as psychiatric 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. This integrative approach has been exciting and has allowed me to move my science beyond correlation to explore causative relationships. I have multiple active projects and grants related to discovering different aspects of stress and drug induced behavioral pathologies. Broadly, my goal is to continue to probe causative mechanisms of modulation in the brain. In addition, via a collaboration with Bryan Roth, I am working to develop new chemical genetic tools that will allow for a more refined dissection of how signaling in the brain can alter behavior.

B. Positions and Honors

Positions

2000-2004 Ph.D. in Neuroscience, Mentor: Neil L. Harrison, Ph.D.
Weill Graduate College of Biomedical Science, Cornell University
2004-2008 Post-doctoral Research Fellow, Mentor: Danny G. Winder, Ph.D.
Department of Molecular Physiology and Biophysics ,Vanderbilt University
2008 - 2009 Research Instructor, Department of Molecular Physiology and Biophysics, Vanderbilt University
2009-Current Assistant Professor, Department of Pharmacology
Bowles Center for Alcohol Studies, University of North Carolina Chapel Hill

Honors

2011 White House Presidential Early Career Award for Scientists and Engineers
2013 Research Society for Alcoholism Young Investigator Award
2014 ACNP Associate Member
2014 UNC Neuroscience Program Mentor of the Year
2014 NARSAD Independent Investigator Award

Other Experience and Professional Memberships

2001- Member, Society for Neuroscience
2006- Member, Research Society for Alcoholism

2011-13 NIH Peer Review Committee: MNPS Ad hoc
2014- NIH Peer Review, MNPS Member
2015- Editorial Board, Molecular Pharmacology

C. Contribution to Science

1. **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.

    c. **Kash TL**, Kim T, Trudell JR and Harrison NL. Evaluation of a proposed mechanism of ligand-gated ion channel activation in the GABAA and glycine receptors. Neurosci Lett. 2004;371(2-3):230-234.

    d. Keramidas A, **Kash TL** and Harrison NL. The pre-M1 segment of the alpha1 subunit is a transduction element in the activation of the GABAA receptor. J Physiol. 2006;575(Pt 1):11-22.

2. **ALCOHOL/STRESS REGULATION OF GLUTAMATE TRANSMISSION** As I entered my postdoc, I changed my focus, moving from examining the structure and function of ion channels, to understanding how alcohol modulated ion channel function in neurons. This is a critical problem and field, as understanding the actions of both acute and chronic alcohol can provide insight to treatment. In particular, I focused my efforts on the actions of alcohol on NMDAR function. Initially, I looked in the BNST, a region known to be important for anxiety and stress related behaviors. I found that alcohol inhibited NMDAR function via selective interaction with NR2B subunits, and that chronic alcohol lead to increased NR2B levels, indicative of a metaplastic state. Moving beyond that, I have continued this effort with my collaborator, Andrew Holmes, where we have additionally shown a dynamic reduction in NMDA function in the PFC, which has important implications for alcohol mediated cognitive dysfunction. Holmes and I have continued this collaboration focusing on gene by environment interactions that shape excitatory transmission and behavior.

    a. **Kash TL**, Matthews RT and Winder DG. Alcohol inhibits NR2B-containing NMDA receptors in the ventral bed nucleus of the stria terminalis. Neuropsychopharmacology. 2008;33(6):1379-1390.

    b. **Kash TL**, Baucum AJ, 2nd, Conrad KL, Colbran RJ and Winder DG. Alcohol exposure alters NMDAR function in the bed nucleus of the stria terminalis. Neuropsychopharmacology. 2009;34(11):2420-2429.

    c. Holmes A, Fitzgerald PJ, MacPherson KP, DeBrouse L, Colacicco G, Flynn SM, Masneuf S, Pleil KE, Li C, Marcinkiewcz CA, **Kash TL**, Gunduz-Cinar O and Camp M. Chronic alcohol remodels prefrontal neurons and disrupts NMDAR-mediated fear extinction encoding. Nat Neurosci. 2012;15(10):1359-1361.

    d. Masneuf S, Lowery-Gionta E, Colacicco G, Pleil KE, Li C, Crowley N, Flynn S, Holmes A and **Kash T**. Glutamatergic mechanisms associated with stress-induced amygdala excitability and anxiety-related behavior. Neuropharmacology. 2014;85:190-197.

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. Subsequent experiments in my own lab have begun to explore cell type genetic modulation of these systems and have contributed widely to understanding how these compounds can exert their effects on behavior.

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. Pleil KE, Lopez A, McCall N, Jijon AM, Bravo JP and **Kash TL.** Chronic stress alters neuropeptide Y signaling in the bed nucleus of the stria terminalis in DBA/2J but not C57BL/6J mice. Neuropharmacology. 2012;62(4):1777-1786.

4. **CIRCUIT ANALYSIS OF BINGE-LIKE 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.

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.

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. Sparrow AM, Lowery-Gionta EG, Pleil KE, Li C, Sprow GM, Cox BR, Rinker JA, Jijon AM, Pena J, Navarro M, **Kash TL** and Thiele TE. Central neuropeptide Y modulates binge-like ethanol drinking in C57BL/6J mice via Y1 and Y2 receptors. Neuropsychopharmacology. 2012;37(6):1409-1421.

d. Cox BR, Olney JJ, Lowery-Gionta EG, Sprow GM, Rinker JA, Navarro M, **Kash TL** and Thiele TE. Repeated cycles of binge-like ethanol (EtOH)-drinking in male C57BL/6J mice augments subsequent voluntary EtOH intake but not other dependence-like phenotypes. Alcohol Clin Exp Res. 2013;37(10):1688-1695.

5. **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. I have an ongoing collaboration with two leaders in these fields, Garret Stuber and Bryan Roth, that has yielded exciting discoveries. With the Stuber group, we utilized optogenetic methods to demonstrate how distinct but overlapping circuits in the BNST can regulate motivational states. With the Roth Lab, we have worked on designing new chemogenetic tools for improved circuit analysis. One of these, the KOR DREADD was recently published. This is a revolutionary new approach that will allow multiplexed chemogenetic control of distinct neurons in vivo. Finally, particularly germane to this proposal, we have focused much of our effort on understanding the impact of alcohol on the serotonin system with particular focus on the BNST. These studies together highlighted the potential 1-2 punch of alcohol exposure, increasing the function of 5HT neurons, and also upregulating the excitatory 5HT2C receptor. This provides critical mechanistic insight in to the clinical observations that some populations of patients show increased anxiety and alcohol consumption in response to SSRIs.

a. Jennings JH, Sparta DR, Stamatakis AM, Ung RL, Pleil KE, **Kash TL** and Stuber GD. Distinct extended amygdala circuits for divergent motivational states. Nature. 2013;496(7444):224-228.

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

c. Lowery-Gionta EG, Marcinkiewcz CA and **Kash TL**. Functional alterations in the dorsal raphe nucleus following acute and chronic ethanol exposure. Neuropsychopharmacology. 2015;40(3):590-600.

d. 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.

My NCBI Bibliography:

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

D. Research Support

R01AA019454-01A1 (PI: Kash) 8/5/10 – 09/30/16
NIH/NIAAA:: *The Role of Serotonin in Alcohol-Withdrawal Induced Anxiety*
Role: PI
Goals: The goal of this project is to test the hypothesis that alterations in 5HT function underlie alcohol withdrawal induced anxiety. NOTE: This reward received a 1.25 year extension as result of the PECASE.

U01MH105892-01 (MPI Submission: Roth, Kash, Jian) 9/30/14 - 8/31/17
NIH BRAIN Initiative: DREADD 2.0: An Enhanced Chemogenetic Toolkit
Role: Co-PI

U01 AA020911 (PI: Kash) 2/10/12 – 1/31/17
NIH/NIAAA: Chronic Alcohol Induced Dysregulation of Central Anti-Stress Systems
Role: PI

5P60AA011605-16 (Crews) 12/01/12 – 11/20/17
NIH/NIAAA: Molecular and Cellular Pathogenesis in Alcoholism
Role: Co-PI of Component 4
Goals: Deconstructing CRF circuits that modulate binge ethanol intake –Res Comp 4

5P60AA011605-16 (Crews) 12/01/12 – 11/20/17
NIH/NIAAA
Molecular and Cellular Pathogenesis in Alcoholism Scientific Core
Role: Co-Director of Neural Circuits Core

1R01 AA022048-01 (Thiele) 7/15/13 – 5/31/18
NIH/NIAAA: The Role of CRF in Binge-Like Ethanol Drinking
Role: Co-PI

NARSAD (PI: Kash) 9/2014 – 9/2016
Role: PI
Dynorphin regulation of plasticity in amygdalar circuits: a role in affective disorders