BIOGRAPHICAL SKETCH

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NAME: Sweeney, Patrick

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

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
University of Rochester, Rochester , New York	BA	05/2012	Psychology
SUNY Upstate Medical University, Syracuse, New York	PHD	03/2017	Neuroscience
University of Michigan, Ann Arbor, Michigan	Postdoctoral Fellow	08/2021	Neuroendocrinology
University of Illinois at Urbana-Champaign, Urbana, Illinois	Assistant Professor	Current	Neuroscience and Physiology

A. Personal Statement

My main research interests include neuronal regulation of feeding, energy homeostasis, and emotional behaviors. During graduate school, I utilized optogenetic and chemogenetic approaches to manipulate neural circuits involved in feeding behavior. In particular, my studies focused on investigating how the neural circuits controlling feeding interact with neural circuits controlling emotional processes. These studies resulted in the discovery of multiple functional neural circuits that regulate feeding and were published (see below) in three first authors publications.

During my postdoctoral work I have focused on deciphering the role of the neuronal melanocortin 3 receptor (MC3R) in energy homeostasis, emotion, and motivation. We have discovered that nearly 100% of hypothalamic AgRP neurons contain the MC3R, and that this receptor is expressed more frequency and at a greater abundance in orexigeneic AgRP neurons than anorexigenic POMC neurons. Consistently chemogenetic activation of MC3R containing neurons in the arcuate nucleus phenocopies AgRP neuronal effects on feeding and anxiety, and MC3R specific compounds potently regulate feeding by engaging AgRP neural circuity, with MC3R agonists stimulating feeding and antagonists suppressing feeding. We also demonstrated that MC3R KO mice exhibit multiple features common to human anorexia nervosa, such as sexually dimorphic feeding and anxiety phenotypes. These findings were recently published in Science Translational Medicine.

Recently, we discovered that mice lacking the MC3R display prolonged anorexia and weight loss in response to fasting, caloric restriction, or administration of anorexigenic drugs. Given the profound anorexigenic effects resulting from pharmacological inhibition of MC3R, current experiments in the laboratory are focused on determining the utility of MC3R antagonism as a weight loss agent and testing the utility of MC3R inhibition as a means to prevent weight re-gain in obesity. We are also utilizing single cell endomicroscopic calcium imaging to determine the cellular and molecular mechanism(s) by which inhibition of MC3R produces anorexia and enhanced weight loss. My long term career goal is to continue this line of research in an independent research program focusing on the central MC3R neural circuits regulating feeding, emotion, and motivation, with the goal of developing novel therapeutics for diseases with co-morbid metabolic and emotional pathologies, such as obesity and anorexia nervosa.

1. Sweeney P, Bedenbaugh MN, Maldonado J, Pan P, Fowler K, Williams SY, Gimenez LE, Ghamari-Langroudi M, Downing G, Gui Y, Hadley CK, Joy ST, Mapp AK, Simerly RB, Cone RD. The melanocortin-3 receptor is a pharmacological target for the regulation of anorexia. Science Translational Medicine. 2021 April 21; 13 (590).

2. Sweeney P, Chen C, Rajapakse I, Cone RD. Network dynamics of hypothalamic feeding neurons. PNAS. 2021 April 6; 118 (14).

3. Ghamari-Langroudi M, Cakir I, Lippert RN, Sweeney P, Litt MJ, Ellacott KLJ, Cone RD. Regulation ofenergy rheostasis by the melanocortin-3 receptor. Sci Adv. 2018 Aug;4(8):eaat0866. PubMed PMID:30140740; PubMed Central PMCID: PMC6105298.

4. Sweeney P, Yang Y. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. Nat Commun. 2015 Dec 15;6:10188. PubMed PMID: 26666960; PubMed Central PMCID:PMC4682174.

B. Positions and Honors

Positions and Employment

2010 - 2011	Research Technician , University of Rochester, Rochester , NY
2012 - 2017	Research Fellow, SUNY Upstate Medical University, Syracuse , NY
2017 -	Postdoctoral Fellow, University of Michigan , Ann Arbor , MI

Other Experience and Professional Memberships

2013 - 2014	Vice President-College of Graduate Studies, SUNY Upstate Student Government
2016 -	Member, Society for Neuroscience
2019 -	Member, Keystone Symposia Conference Assistant

Honors

2010	Summer Scholars Program , University of Rochester
2010	Schmitt Program on Integrative Brain Research, University of Rochester
2011	Summer Undergraduate Research Fellowship, SUNY Upstate Medical University
2016	Oral Presentation Award, SUNY Upstate Medical University College of Graduate Studies
2017	John Bernard Henry Endowed Scholarship Award, SUNY Upstate Medical University
2019	Top Overall Presentation by Graduate Student or Postdoctoral Fellow, University of Michigan Life Sciences Institute Departmental Retreat

Contribution to Science

1. The ventral hippocampus was previously known to be involved in feeding and energy homeostasis. However, until recently, the specific cell types and neural circuits mediating the role of the hippocampus in feeding behavior remained largely unknown. During graduate school I utilized modern optogenetic and chemogenetic approaches to selectively determine the neural pathways that mediate the role of ventral hippocampus in feeding behavior. In summary, we found that ventral hippocampus suppresses feeding via interactions with the lateral septum. We further dissected neural pathways connecting neurons in the septum with the lateral hypothalamus or paraventricular hypothalamus, brain regions with a major role in homeostatic and hedonic control of feeding behavior. Together these findings provided valuable insight into neural circuit interactions between the hippocampal formation and feeding circuitry.

   a. Sweeney P, Li C, Yang Y. Appetite suppressive role of medial septal glutamatergic neurons. Proc Natl Acad Sci U S A. 2017 Dec 26;114(52):13816-13821. PubMed PMID: 29229861; PubMed

Central PMCID: PMC5748170.

b. Sweeney P, Yang Y. Neural Circuit Mechanisms Underlying Emotional Regulation of Homeostatic Feeding. Trends Endocrinol Metab. 2017 Jun;28(6):437-448. PubMed PMID: 28279562; PubMed Central PMCID: PMC5438765.

c. Sweeney P, Yang Y. An Inhibitory Septum to Lateral Hypothalamus Circuit That Suppresses Feeding. J Neurosci. 2016 Nov 2;36(44):11185-11195. PubMed PMID: 27807162; PubMed Central PMCID: PMC5148238.

d. Sweeney P, Yang Y. An excitatory ventral hippocampus to lateral septum circuit that suppresses feeding. Nat Commun. 2015 Dec 15;6:10188. PubMed PMID: 26666960; PubMed Central PMCID: PMC4682174.

2. Research focusing on central nervous system control of feeding behavior has primarily addressed the role of neurons and neural circuits in feeding behavior. However, the role of non-neuronal cells, such as astrocytes, in feeding behavior has remained understudied. For this reason, during graduate school I utilized optogenetic approaches to selectively manipulate astrocytes within the medial basal hypothalamus, a brain region with a major role in feeding behavior and energy homeostasis. We found that stimulation of astrocytes reduces feeding in a frequency dependent manner with higher frequency stimulation producing progressively larger reductions in feeding behavior. These findings added to the growing body of literature implicating astrocytes in central nervous system control of feeding and energy homeostasis.

   a. Sweeney P, Qi Y, Xu Z, Yang Y. Activation of hypothalamic astrocytes suppresses feeding without altering emotional states. Glia. 2016 Dec;64(12):2263-2273. PubMed PMID: 27658520.

3. The central melanocortin receptors (melanocortin 3 receptor and melanocortin 4 receptor) are critically involved in regulating energy homeostasis and feeding behavior. While the role of the MC4R in energy homeostasis is well established, the specific role of the MC3R in energy homeostasis has remained enigmatic. During my postdoctoral studies in the Cone lab I utilized chemogenetics and mouse behavioral assays to dissect the role of different MC3R expressing neurons in feeding behavior. These experiments revealed that MC3R expressing neurons in the arcuate nucleus of the hypothalamus stimulate feeding, while MC3R expressing neurons in the paraventricular thalamic nucleus suppress feeding. This data provided additional experimental evidence supporting a bidirectional role for the MC3R in controlling the upper and lower bounds of energy homeostasis (energy rheostasis). We have also developed a *in vivo* imaging system for monitoring the activity of MC4R circuitry in real time in awake behaving animals (Inscopix miniaturized microscope). This approach will provide a novel system for studying how the central melanocortin system impacts feeding circuitry throughout the brain.

   a. Sweeney P, Bedenbaugh MN, Maldonado J, Pan P, Fowler K, Williams SY, Gimenez LE, Ghamari-Langroudi M, Downing G, Gui Y, Hadley CK, Joy ST, Mapp AK, Simerly RB, Cone RD. The melanocortin-3 receptor is a pharmacological target for the regulation of anorexia. Science Translational Medicine. 2021 April 21; 13 (590).

   b. Sweeney P, Chen C, Rajapakse I, Cone RD. Network dynamics of hypothalamic feeding neurons. PNAS. 2021 April 6; 118 (14).

   c. Ghamari-Langroudi M, Cakir I, Lippert RN, Sweeney P, Litt MJ, Ellacott KLJ, Cone RD. Regulation of energy rheostasis by the melanocortin-3 receptor. Sci Adv. 2018 Aug;4(8):eaat0866. PubMed PMID: 30140740; PubMed Central PMCID: PMC6105298.

C. Additional Information: Research Support and/or Scholastic Performance

Ongoing Research Support

1K99DK127065, NIDDK
Sweeney, Patrick (PI) 09/01/2020-current
MC3R inhibition as a strategy to maintain weight loss in obesity
Role: PI

Brain and Behavior Research Foundation (BBRF) Young Investigator Grant
Sweeney, Patrick (PI) 01/01/2022-01/01/2024
Melanocortin 3 receptor agonism as a preventative therapy for stress-induced anorexia, anxiety, and anhedonia
Role: PI

1F32HD095620-01, NICHD
Sweeney, Patrick (PI) 03/01/18-08/31/2020
A role for hypothalamic melanocortin 3 receptors in integrating energy state with reproductive physiology
Role: PI

Life Sciences Institute (LSI) Cubed Funding
Sweeney, Patrick (PI) 03/01/19-03/01/20
Functional imaging of the activity patterns of orexin neurons related to breathing, and examination of how it is affected by obesity
Role: PI