Name: Paul Kenny
PI Name: Paul Kenny
Email: paul.kenny@mssm.edu
PI email: paul.kenny@mssm.edu

Brain-body chemosensing regulates the addictive properties of nicotine

Stephanie P.B. Caligiuri[1], Purva Bali[1], Maria Vittoria Micioni Di Bonaventura[1,2], Jianxi Liu[1], Zoe Whalen[1], Vi Tuong To1, Nikolaos Tzavaras[1,3], Maya Williams[1], Richard M. O'Connor[1], Mary. P Heyer[1], Vanessa E. Lehmann[1], Victor Mathis[1], Kristin Beaumont[4], Robert B. Sebra[4], and Paul J. Kenny1

[1]Nash Family Department of Neuroscience, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [2]School of Pharmacy, Pharmacology Unit, University of Camerino, Camerino, Italy; 3Microscopy CoRE, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA; [4]Department of Genetics and Genomic Sciences, Icahn School of Medicine at Mount Sinai, New York, NY 10029, USA.

Background: Nicotine is thought to act on brain motivation circuits exclusively through neuronal nicotinic receptors (expressed by neurons in these circuits. Nicotine is a plant-derived alkaloid, a class of compound often noxious or poisonous to humans. Alkaloids have an innately aversive bitter taste, a sensory modality that evolved to protect against ingestion of potentially noxious substances. Taste 2 (bitter) receptors (T2Rs) are activated by alkaloid compounds and serve as "poison detectors". **Rationale/significance**: Allelic variation in T2R genes can increase vulnerability to tobacco dependence and other substance use disorders (SUDs), but little is known about T2R involvement in SUDs. **Hypothesis:** We hypothesized that nicotine (and other addictive alkaloid drugs) is "sensed" by T2Rs to elicit noxious sensory responses, which protects against addiction. **Results:** We show that nicotine engages T2R signaling in an α-gustducin (*Gnat3*)-dependent manner. Whole-animal fluorescence imaging and polysynaptic virus tracing identified a T2R-regulated projection from oral cavity to solitary tract nucleus (NTS) and fourth ventricle choroid plexus (4-ChP) in hindbrain that is activated by nicotine. Chemogenetic inactivation of this sensory system, or genetic perturbation of T2R signaling, attenuated noxious response to nicotine to increase nicotine reward. Single cell RNA sequencing identified T2R-dependent transcriptional responses to nicotine in NTS and 4-ChP. CRISPR-mediated disruption of nicotine-induced signaling in 4ChP attenuated nicotine aversion and increased nicotine reward/intake. **Discussion:** Taste-relevant sensory input to choroid plexus drives nicotine avoidance behaviors, suggesting that ChP signaling may protect against nicotine addiction and other SUDs.