Yong Xu, MD, PhD
Professor
Pediatrics & Molecular and Cellular Biology

*A Hyperactive Midbrain Circuit Triggers Anorexia*

Yong Xu (M.D. &Ph.D.) received his medical training in Tongji Medical University (China) and then Ph.D. training in University of Alberta (Canada). After a postdoctoral training at the University of Texas Southwestern Medical Center (Dallas), he established his own research program at Baylor College of Medicine in 2010. The major goals of Dr. Xu's lab are to identify the novel neural circuits, neurotransmitters and intracellular molecules in the brain that are critical for control of feeding behavior and metabolism. Specifically, Dr. Xu generates unique mouse models, using Cre-loxP/Flp-frt strategy, with genes of interest manipulated in specific populations of neurons at the time of choice. Dr. Xu uses these models, in combination of the modern chemogenetics/optogenetics, fiber photometry and electrophysiology, to establish the physiological relevance of specific neural networks in the regulation of energy homeostasis, glucose balance and behaviors. Dr. Xu's research has been continuously funded by various sources, including several NIH awards (e.g. K99/R00, R01, P01) and funds from USDA, AHA, ADA and other private foundations (Klarman). Dr. Xu's work has resulted in papers in Nature (2021), Nature Neuroscience (2010, 2019), Nature Medicine (2017), Nature Communications (2018, 2019, 2020, 2021), Nature Metabolism (2020), Science Translational Medicine (2021), Journal of Clinical Investigation (2013, 2014, 2015, 2017, 2019), Molecular Psychiatry (2020, 2021), Translational Psychiatry (2021), Cell Reports (2015, 2016, 2017), Hypertension (2016), Neuron (2008, 2011), Cell Metabolism (2010, 2011, 2013, 2013), PNAS (2011, 2020), Biological Psychiatry (2016), Journal of Neuroscience (2010, 2014 and 2015), Diabetes (2015, 2016).

Abstract: The midbrain dopamine (DA) and serotonin (5-HT) neurons are believed to interact to regulate various motivated behaviors, including feeding, but these two systems are often studied separately. Here we found that DA neurons in the ventral tegmental area (VTA) regulate the activity of 5-HT neurons in the dorsal Raphe nucleus (DRN) in a bidirectional fashion, either a low strength-induced inhibition mediated by D2 dopamine receptor (DRD2), or a high strength-induced activation mediated by D1 dopamine receptor (DRD1). Strikingly, the DRD2 or DRD1-mediated $DA^{VTA}$→DRN neurotransmission results in overeating or anorexia in mice, respectively. Further, in the activity-based anorexia, a

mouse model mimicking some clinical features of human anorexia nervosa (AN), we observed a DRD2→DRD1 shift of DA neurotransmission on 5-HT$^{DRN}$ neurons, which causes a constant activation of these neurons and contributes to AN-like behaviors. Finally, we found that systemic administration of a DRD1 antagonist can prevent anorexia and weight loss. Our results revealed an interesting strength-dependent role of a midbrain circuit in feeding control, which may underlie the pathophysiology of human anorexia nervosa and represent a rational target for treatment.