2023 IMPACT CIRCLE

Project Title: **In Search of a Meditation Pill: Aging Better by Tuning the Sympathetic Nervous System**

Investigator(s) and collaborations: **Pejmun Haghighi, PhD**

Unmet Need/Primary Question:
Understanding the mechanisms that promote the maintenance of cellular and tissue homeostasis is perhaps the most critical goal of aging research. A large body of experimental evidence suggests that a major regulator of functional homeostasis of our organs is the autonomic nervous system. Divided into two parts the sympathetic (for fight or flight) and parasympathetic (for rest and digest), the autonomic nervous system is arranged into distinct ganglia (collection of nerve cells) that receive input from the central nervous system and send axons into all bodily organs, including heart, liver, lung, intestine, fat and many other tissues (Fig. 1A). The balance between sympathetic and parasympathetic activity regulates the majority of our vital functions, including heart rate, blood pressure, sweating, body temperature, kidney function, gastrointestinal function, fat tissue metabolism and many more. Failure of this regulation is associated with a number of metabolic and chronic diseases including diabetes, obesity, high blood pressure and cardiovascular disease. And yet, the involvement of the autonomic nervous system in age-related functional decline remains largely unexplored. We propose to use a combination of genetic and pharmacological approaches to a) generate a genetic model for studying the role of autonomic/sympathetic function in aging mice and b) generate/identify novel pharmacological tools to tune sympathetic function with the ultimate goal of maintaining and extending organismal healthspan during aging.

Novel Hypothesis:
Sympathetic neurons receive input via preganglionic neurons emerging from the spinal cord (Fig. 1B). The main neurotransmitter released at preganglionic terminals is acetylcholine (ACh), which binds to postsynaptic neuronal nicotinic acetylcholine receptors (nAChR) expressed on sympathetic neurons. This will activate sympathetic neurons ultimately leading to the release of noradrenaline/norepinephrine (NA) at sympathetic neuron terminals innervating numerous tissues (Fig. 1C). Adrenergic receptors (ADRs) expressed in target organs (fat tissue, vasculature, heart, kidney and etc) then transduces the effect of NA release, leading to a host of actions: elevation of heart rate, constriction of vessels and increase in blood pressure, suppression of blood flow to the stomach, dilation of bronchioles and increase breathing and so on.

Our overarching hypothesis is that limiting/tuning down sympathetic drive will have beneficial effects for organismal homeostasis in aging organisms and in response to

chronic stress. While in response to acute stress elevation of sympathetic drive can be beneficial to the organism and trigger survival mechanisms (fight or flight), we believe, based on a large body of experimental evidence, increased sympathetic drive under chronic conditions and during aging can be detrimental to organ function and organismal healthspan. In addition, many of us have experienced the beneficial effects of meditation in our everyday life, which is thought to act largely by suppressing the sympathetic fight or flight response.

Project Proposal:

a) Our first goal is to take advantage of the 3 nAChR knock out mice to develop a powerful genetic model to test the role of sympathetic drive under metabolic stress of high fat diet. Multiple lines of evidence indicate that high fat diet induced obesity and metabolic stress are accompanied by an increase in sympathetic drive in animal models, as manifested by cardiovascular dysfunction among other symptoms. We will directly test the role of sympathetic drive by disrupting sympathetic transmission (3 nAChR knock out mice), in young adult mice (2-3 months old) and middle aged mice (8-12 months old) under 6-8 weeks of high fat diet. We have previously reported that these mice do not exhibit synaptic transmission at the sympathetic ganglion and have much reduced sympathetic drive in multiple organs. By placing these mice in a metabolic cage, we will be able to monitor multiple vital functions and metabolic readouts, addressing the role of sympathetic drive.
b) The autonomic nervous system is subject to chronic insults by the many stressors encountered in daily life, and by the off-target actions of many of the most commonly prescribed drugs including β-blockers, statins, calcium channel blockers, ACE or Angiotensin II inhibitors among others, many of which are prescribed for lifelong use in patients. Parallel to the development of the model above, we plan to test novel candidate molecules as pharmacological tools to inhibit/limit the sympathetic drive under disease or during aging. In particular, we have uncovered a novel function for polyamines and polyamine derived molecules in tuning sympathetic transmission. Our findings show that neuronal nAChRs, which are responsible for signal transduction in sympathetic nerves (Fig. 1B), can be blocked by polyamines and derivatives at concentration as low as nano molar range. These experiments were conducted in heterologous cells, where we constituted nAChRs in vitro and tested their activity in the presence or absence of polyamine blockers using direct electrophysiological measurements. As emerging data in flies and mice suggest a beneficial role for polyamines in promoting lifespan and healthspan, we are excited to test the role polyamines and derivatives in regulating sympathetic activity in aging mice, with the hope of discovering a meditation pill! In parallel with experiments described in a) we will test the consequence of high fat diet in control and 3 nAChR knockout mice while administering polyamine based molecules vs vehicle.

Expected results: If our hypothesis that increased sympathetic drive is responsible for mediating the negative effects of high fat diet is correct, we predict that 3 nAChR knockout mice will show fewer metabolic and cardiovascular defects associated with high fat diet because of the reduction in sympathetic drive. Similarly, we predict that administering polyamine derived molecules will protect mice against the negative consequences of high fat diet. However, if the beneficial effect of polyamines is due to their inhibitory action of nAChRs, we predict that (3 nAChR knock out mice will not

respond to these drugs, as these mice have already reduced sympathetic activity. We believe our results will build a steppingstone for future experiments aimed at understanding the role of sympathetic function in aging through longitudinal studies with funding from the National Institute of Aging.

Description of Potential Impact:
The studies proposed here will provide a conceptual advance for our understanding of autonomic function during aging and disease while paving the way for the design of new pharmaceuticals aimed at maintaining functional homeostasis during aging. Because of its accessibility (not shielded by the blood brain barrier) and its distinct anatomy (situated in distinct ganglia), the autonomic ganglia are ideal for targeting by pharmaceuticals. We believe, new therapeutic approaches that can ultimately tune autonomic function will give rise to a new generation of anti-aging drugs that could potentially revolutionize the aging field.

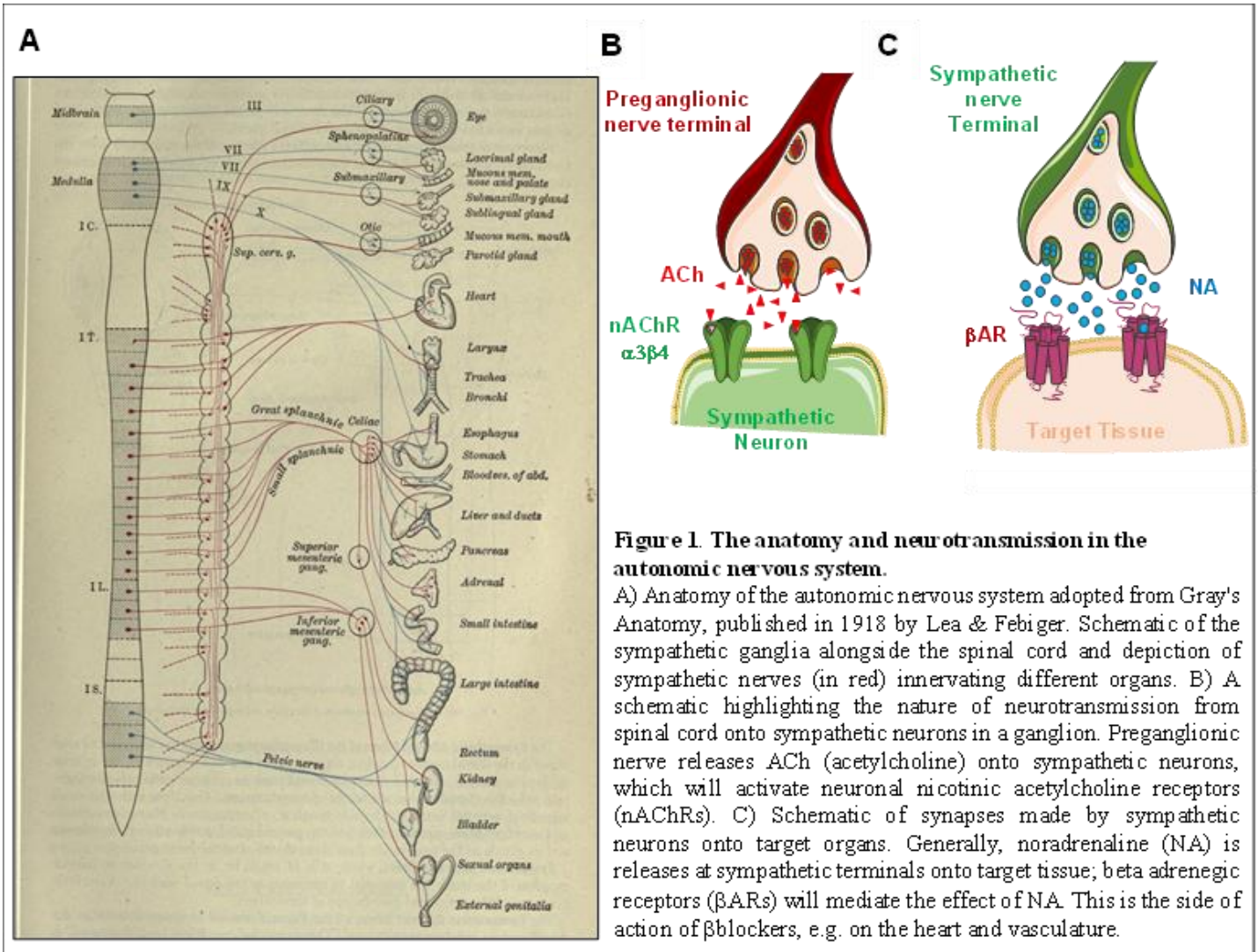

Figure 1. The anatomy and neurotransmission in the autonomic nervous system.
A) Anatomy of the autonomic nervous system adopted from Gray's Anatomy, published in 1918 by Lea & Febiger. Schematic of the sympathetic ganglia alongside the spinal cord and depiction of sympathetic nerves (in red) innervating different organs. B) A schematic highlighting the nature of neurotransmission from spinal cord onto sympathetic neurons in a ganglion. Preganglionic nerve releases ACh (acetylcholine) onto sympathetic neurons, which will activate neuronal nicotinic acetylcholine receptors (nAChRs). C) Schematic of synapses made by sympathetic neurons onto target organs. Generally, noradrenaline (NA) is releases at sympathetic terminals onto target tissue; beta adrenegic receptors (βARs) will mediate the effect of NA. This is the side of action of βblockers, e.g. on the heart and vasculature.