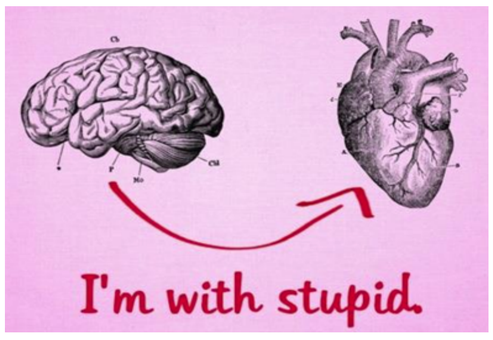
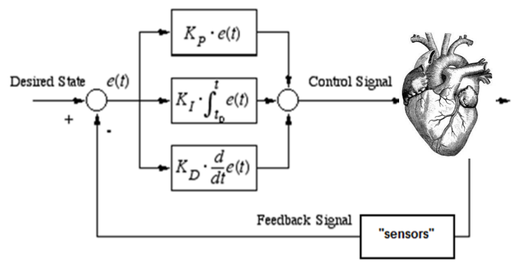
Autonomic Neural Control of the Heart - Schild Laboratory

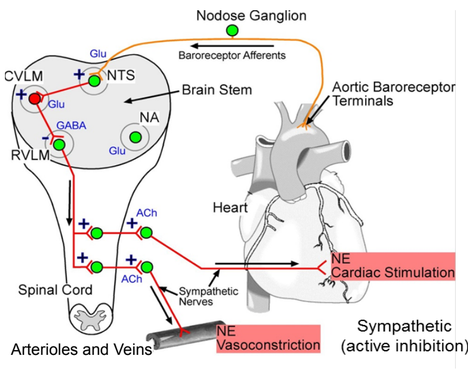
Translational neural engineering: pursuing clinically relevant questions concerning brain control of the heart in both health and disease

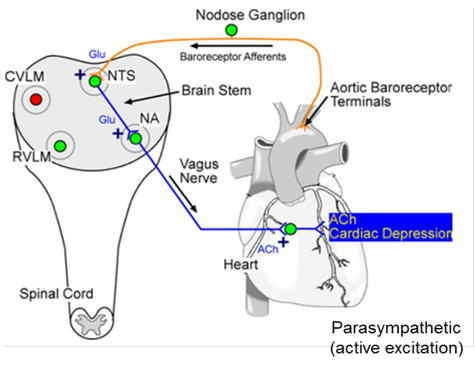
Neurocirculatory control: afferent (sensory) feedback is essential



Negative feeback control of heart rate and blood pressure







Robust control of the cardiovascular system requires two general brain pathways: feedforward, i.e. central commands (efferent) and sensory feedback (afferent), i.e. reflex control. The baroreceptor reflex (BRx) is essential for circulatory homeostasis and regulates heart rate and blood pressure at a level appropriate for each particular behavioral state, e.g. rest, exercise and sleep under healthy and diseased conditions.

Cardiovascular pathologies and baroreflex function: research questions and objectives

Clinical significance of the baroreflex (BRx) is well known:

- Heart failure is a disease categorized by sympathetic hyperactivity, parasympathetic withdrawal, and impaired BRx control of sympathetic activation. (Shen & Zipes, 2015)
- BRx dysfunction is implicated in neurally mediated syncope, dysrhythmias and orthostatic hypotension. (Cortelli, 1994; Armour, 2004; Low, 2015)
- Impaired BRx sensitivity (BRS) and increased heart rate variability (HRV) suggest an increased risk of sudden cardiac death. (Monahan, 2007)

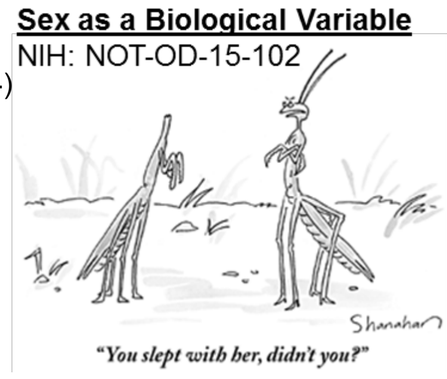
Many clinically relevant questions remain concerning sex (gender) and sympathovagal balance:

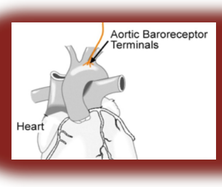
- Major differences in cadiovascular disease exist between men and women. (Regitz-Zagrosek and Kararigas, 2017)
- Parasympathetic markers for HRV and BRS differ between males and females. (Sevre, 2001; Christou, 2003)
- Regulation of cardiovascular function differs between men and women. (Huxley, 2007)

The Schild lab was first to experimentally validate:

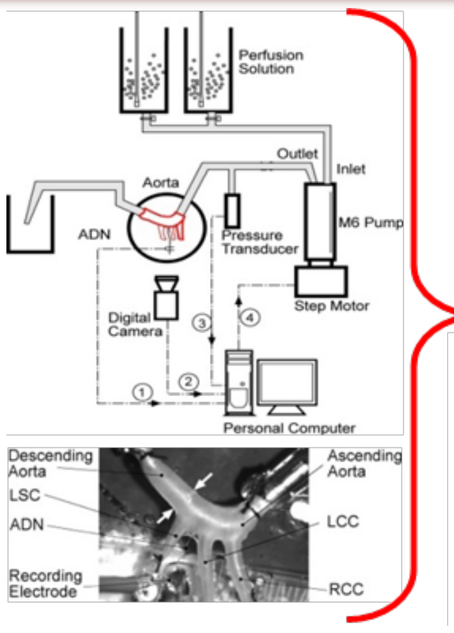
- An afferent explanation for sexual dimorphism in the baroreflex. (2014)
- Differential distribution of voltage-gated channels in myelinated and unmyelinated baroreceptor afferents extends to gender. (2012)
- Electrophysiological and neuroanatomical evidence of sexual dimorphism in baroreceptor neuron function. (2008)

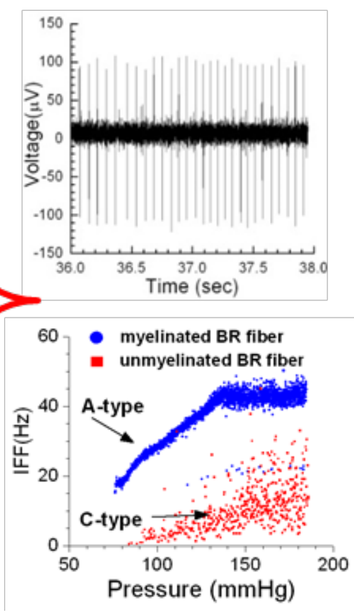
The Schild lab utilizes a synergistic combination of *in vitro*, *in situ* and *in silico* methodologies to study sexual dimorphism in the neural coding of blood pressure dynamics and BRx function.



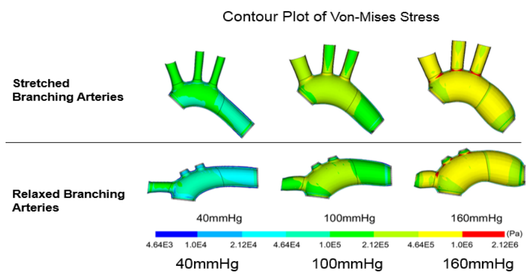


in vitro aortic arch for recording single BR afferent fibers



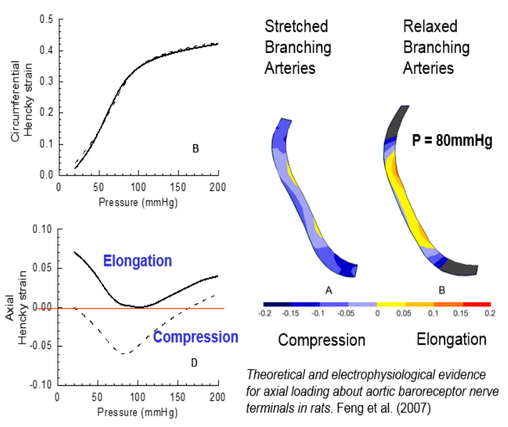


FE Model-Predicted Pressure Deformation



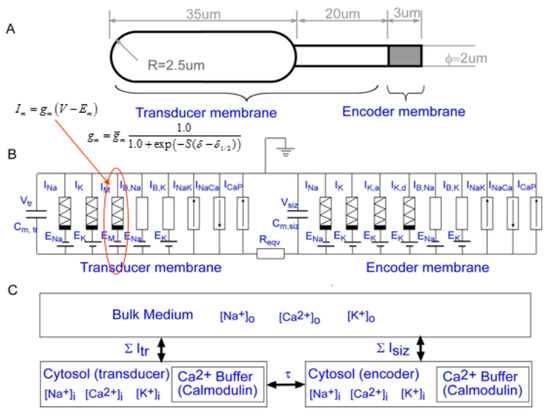
The aortic arch is surgically removed from the animal and cannulated for perfusion and computer control of steady-state intraluminal pressure and pressure ramps (1 mmHg/sec). BR discharge frequency encodes both mean arterial pressure and its derivative (P and dP/dt)

data-directed computational modeling

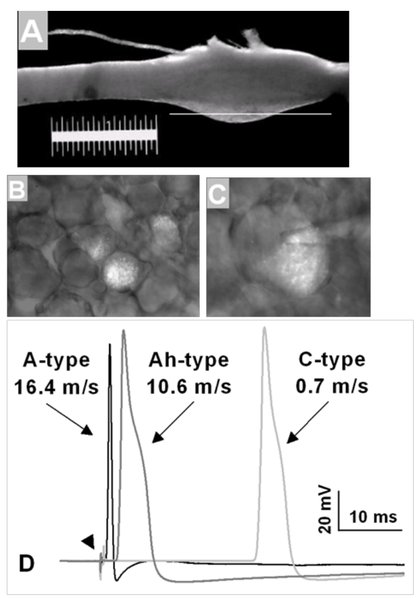


Theoretical and electrophysiological evidence for axial loading about aortic baroreceptor nerve terminals in rats. Feng et al. (2007)

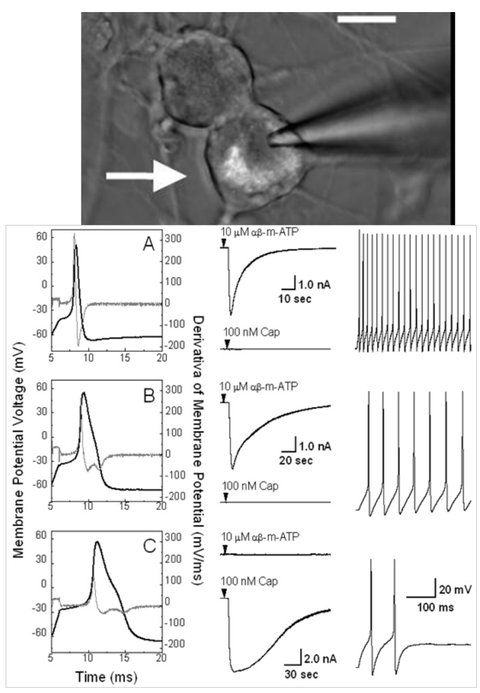
Computational modeling of pressure mechanotransduction and encoding



in vitro patch clamp for electrophysiological study

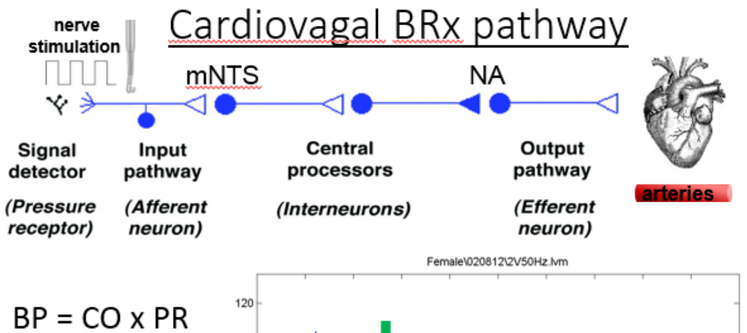


Patch clamp study of identified baroreceptor neurons with intact afferent fibers.
A) vagal ganglia, scale = 1 mm **B)** view inside ganglia with multiple labeled ABN, **C)** patch recording of single ABN, **D)** examples of nerve evoked action potentials from female rat. Arrowhead points to artifact from ADN stimulation.



Patch study of intact and isolated ABN. TOP: isolated and fluorescently labeled (arrow) ABN. Scale bar = 35 μm BOTTOM: using the intact ganglion preparation current injected via the patch electrode evokes somatic action potentials from ABN of known fiber CV.

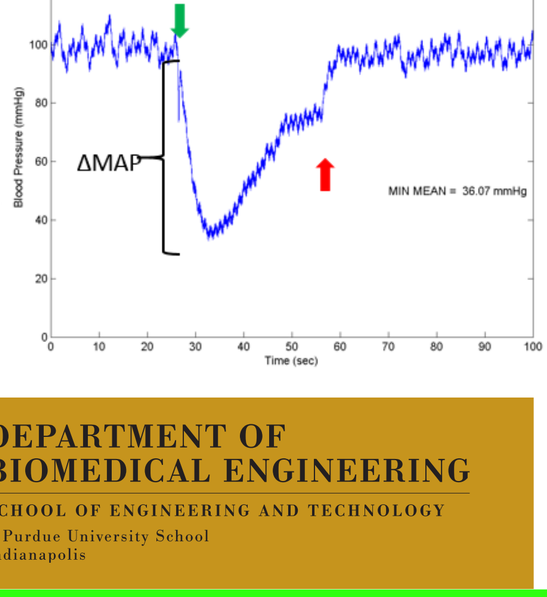
in situ study of the BRX reveals frequency- and sex-dependent differences in central integration of A-type and C-type BR fibers



BP = CO x PR
CO = SV x HR

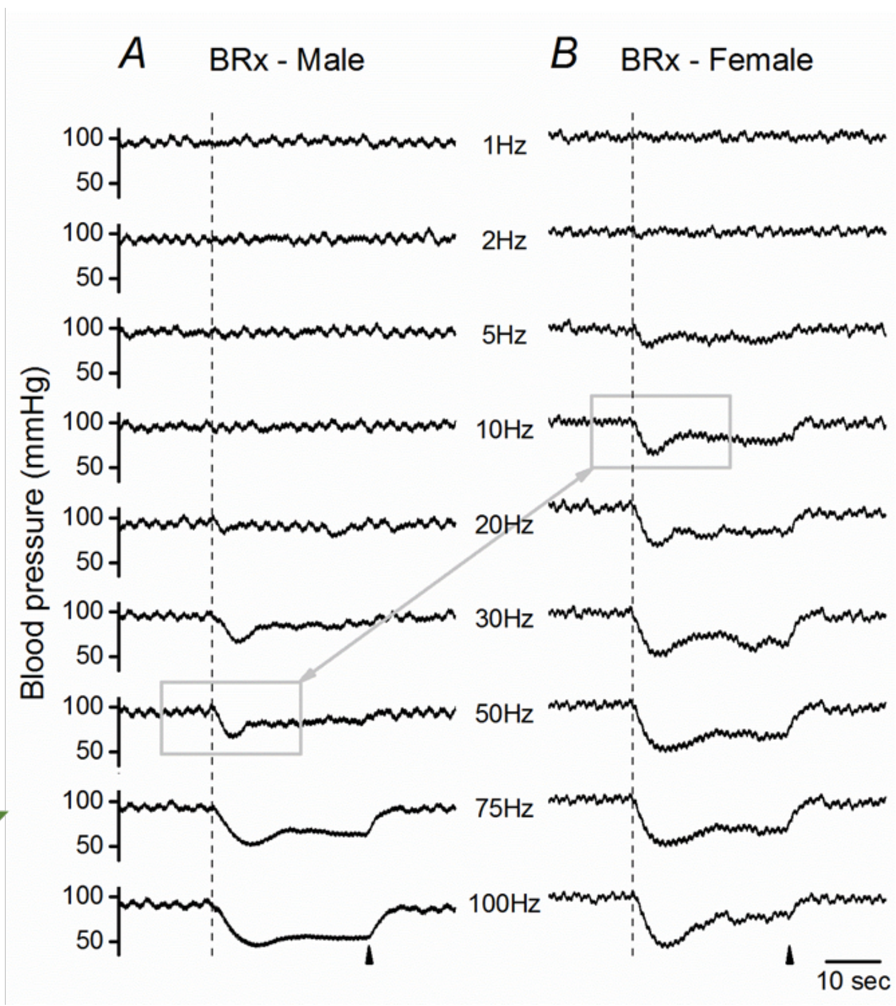
BP = Blood Pressure
CO = Cardiac output
PR = Peripheral resistance
SV = Stroke volume
HR = Heart rate
MAP = mean arterial pressure

MAP decreases w/nerve stimulation



Sex differences in baroreflex (BRx) function are well documented. Hormones likely contribute to this dimorphism, but many functional aspects remain unresolved. Our lab has been investigating a subset of vagal sensory neurons that constitute nearly 50% of the total population of myelinated aortic baroreceptors (BR) in female rats but less than 2% in male rats. Termed "Ah," this unique phenotype has many of the nonoverlapping electrophysiological properties and chemical sensitivities of both myelinated A-type and unmyelinated C-type BR afferents. We utilize three distinct experimental protocols to determine if Ah-type barosensory afferents underlie, at least in part, the sex-related differences in BRx function. Electron microscopy of the aortic depressor nerve (ADN) revealed that female rats have less myelin ($P < 0.03$) and a smaller fiber cross-sectional area ($P < 0.05$) per BR fiber than male rats. Electrical stimulation of the ADN evoked compound action potentials and nerve conduction profiles that were markedly different ($P < 0.01$, n = 7 females and n = 9 males). Selective activation of ADN myelinated fibers evoked a BRx-mediated depressor response that was 3-7 times greater in female (n = 16) than in male (n = 17) rats. Interestingly, the most striking hemodynamic difference was functionally dependent upon the rate of myelinated barosensory fiber activation. Only 5-10 Hz of stimulation evoked a rapid, 20- to 30-mmHg reduction in arterial pressure of female rats, whereas rates of 50 Hz or higher were required to elicit a comparable depressor response from male rats. Collectively, our experimental results are suggestive of an alternative myelinated baroreceptor afferent pathway in females that may account for, at least in part, the noted sex-related differences in autonomic control of cardiovascular function.

Increasing frequency



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