Chronic activation of hypothalamic oxytocin neurons improves cardiac function in a rat model of left ventricular hypertrophy-induced heart failure

Kara Garrott*, Jhansi Dyanavapalli, Mary Kate Dwyer, Edmund Cauley*, Sarah Kuzmiak-Glancy*, Xin Wang+, David Mendelowitz*, Matthew Kay*

*Department of Biomedical Engineering, +Department of Pharmacology and Physiology
The George Washington University

Hypothesis

Activation of parasympathetic vagal neurons within the brainstem could provide a new approach for restoring autonomic balance in HF. We hypothesize that doing so will blunt the progression of HF by slowing the decline of cardiac function.

Background

- A distinctive hallmark of heart failure (HF) is an imbalance of the cardiac autonomic system.
  - Increased sympathetic activity and decreased parasympathetic tone.
- Clinical significance of over-activation of cardiac sympathetic nerves is well established.
- Parasympathetic nerve regulation has received much less attention until recently.

Methods

- Rats underwent trans-ascending aortic constriction (TAC) to induce left ventricular (LV) hypertrophy that progresses to HF.
- In a subset of HF rats, oxytocin (OXT) neurons in the paraventricular nucleus of the hypothalamus were chronically activated by selective expression and activation of excitatory DREADDS receptors (treatment).
- The dose response of excised perfused hearts (n=19) to isoproterenol (β-adrenergic agonist) was measured from age matched control, disease, and treatment animals.
- HR, LV pressure, and coronary flow (CFR) were analyzed to determine if hearts from treated animals had improved function.

Blood OXT and cardiac protein expression

- Plasma OXT was not different between groups, indicating selective activation of cardiac vagal neurons (not global OXT release).
- IL-1β, an inflammatory protein, is elevated in TAC but not in other groups via Western Blotting.
- Western Blots of Collagen III demonstrate an increase in TAC and TAC+OXT.

OXT treatment partially blunts morphological changes induced by HF

- Representative Trichrome images from each group. Top: longitudinal slice of hearts. Middle: H&E staining to measure cell size. Bottom: Trichrome staining. Collagen formation is evident in the disease heart, in blue. B. Myocyte cell surface area was significantly increased in TAC (P<0.05). C. Scar tissue formation was significantly greater in disease hearts (P<0.05).

Functional parameters were depressed in HF rats but improved with OXT treatment

- A. HR was not significantly different between groups (P>0.05).
- Coronary flow rate trended lower in TAC (n=5) in comparison with Control (n=5), TAC+OXT (n=5), and OXT NORM (n=6) (ns, P>0.05).
- LV developed pressure (LVDP) was significantly greater in Control (n=5), TAC+OXT (n=7), and OXT NORM (n=6) hearts than TAC (n=7) (P<0.05). Representative LVDP signals for each group are shown.

Conclusion

- Chronic activation of hypothalamic oxytocin neurons improves cardiac morphology and function, likely by reinstating cardioprotective parasympathetic activity.
- Both chronotropic and inotropic parameters were improved in treated hearts.
- While restoration of parasympathetic activity improved functional parameters, it did so without fully restoring the deficit in β-adrenergic sensitivity in failing hearts.

Acknowledgements

This work was supported by grants from the NIH (R01-HL095828 to M. W. Kay and R01HL133862 to D. Mendelowitz).