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

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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.

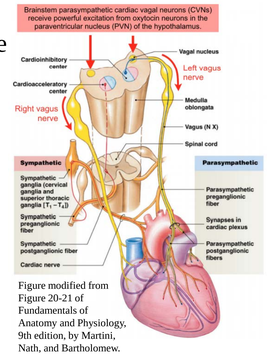
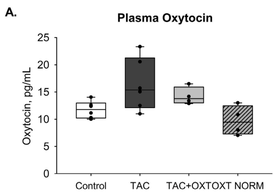


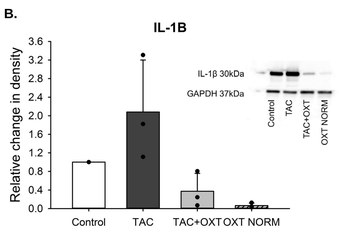
Figure modified from Figure 20-21 of Fundamentals of Anatomy and Physiology, 9th edition, by Martini, Nath, and Bartholomew.

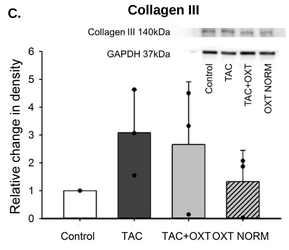
Methods

- 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



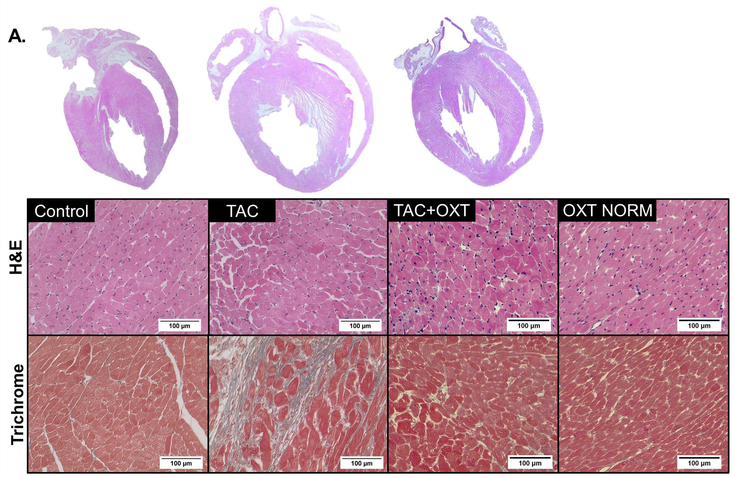


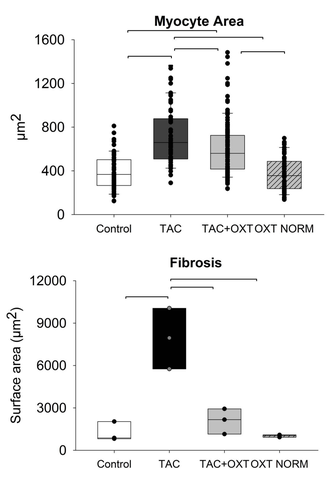


A. Plasma OXT was not different between groups, indicating selective activation of cardiac vagal neurons (not global OXT release)
B. IL-1β, an inflammatory protein, is elevated in TAC but not in other groups via Western Blotting.
C. Western Blots of Collagen III demonstrate an increase in TAC and TAC+OXT.

Experimental groups: Control | TAC | TAC+OXT | OXT NORM

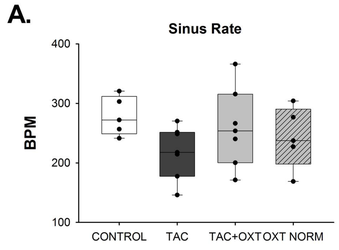
OXT treatment partially blunts morphological changes induced by HF

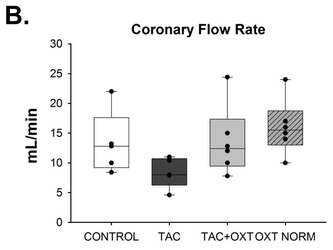




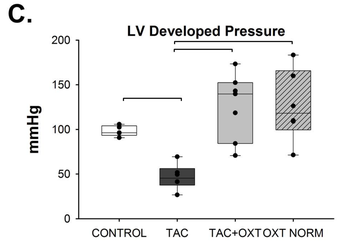
A. Representative Trichrome images from each group. Top: longitudial slice of hearts. Middle: H&E staining to measure cell size. Bottom: Trichrome staining. Collagen formation is evident in the disease heart, in blue. B. Myocyte cell surface area was significantly increased in TAC ($P<0.05$). C. Scar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

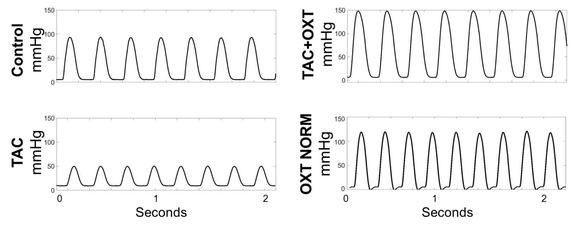
Functional parameters were depressed in HF rats but improved with OXT treatment

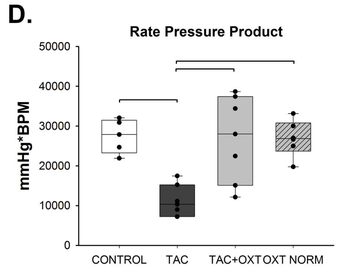


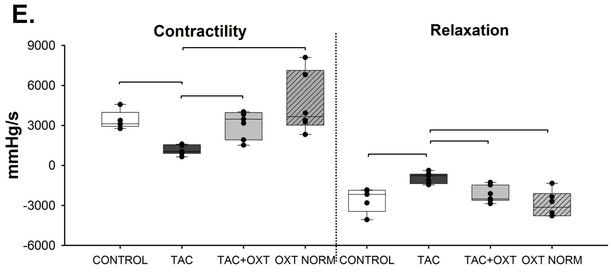


A. HR was not significantly different between groups ($P>0.05$).
B. Coronary flow rate trended lower in TAC (n=5) in comparison with Control (n=5), TAC+OXT (n=5), and OXT NORM (n=6) (ns, $P>0.05$).
C. LV developed pressure (LVDP) was significantly greater in Control (n=5), TAC+OXT (n=7), and OXT NORM (n=6) hearts than TAC (n=7) ($P<0.05$). Representative LVDP signals for each group are shown.
D. Rate pressure product (RPP), a measure of work, was significantly depressed in TAC in comparison with all other groups ($P<0.05$).
E. Both contractility and relaxation were significantly depressed in TAC in comparison to all other groups.

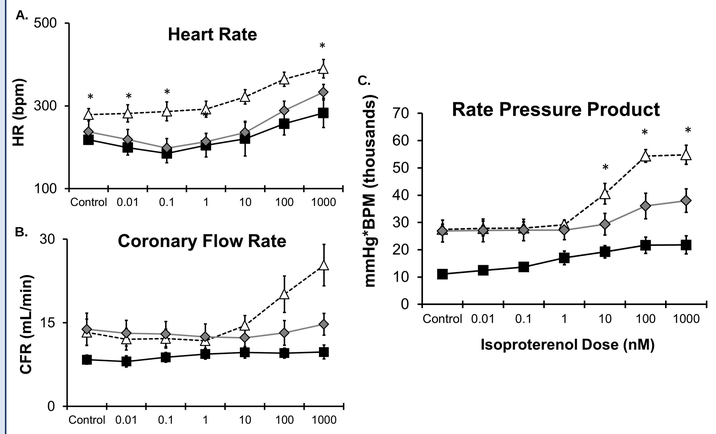




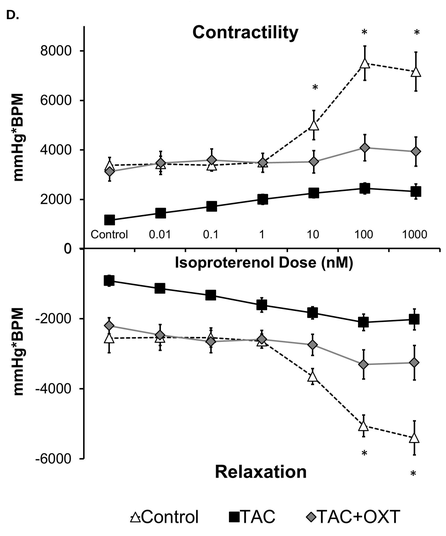




β-adrenergic Stimulation



A. HR increased in all groups with β-adrenergic stimulation. HR remained depressed in disease hearts throughout β-adrenergic stimulation.
B. There were no CFR differences among isoproterenol doses. Treatment CFR was consistently higher than disease CFR.
C. Rate pressure product (RPP) was significantly different between all groups and doses of isoproterenol.
D. Treatment contractility did not increase with isoproterenol dose while control responded to increasing dose with increased contractility.



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

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