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EDITORIAL COMMENT

Oxytocin

A New Therapeutic for Heart Failure?*

Beth A. Habecker, PhD[a,b,c]

Heart failure is a major public health problem, affecting more than 23 million people worldwide. The prevalence of heart failure is increasing throughout the world, driven by a variety of factors including aging populations and increased incidence of hypertension, diabetes, and obesity. Paradoxically, better treatment of coronary artery disease and myocardial infarction has also contributed, as survivors may eventually develop heart failure. Almost one-half of the patients diagnosed with heart failure die within 5 years, highlighting the need for new interventions.

A hallmark of human heart failure is autonomic imbalance, characterized by elevated sympathetic activity and parasympathetic withdrawal. This imbalance contributes to disease progression and is the focus of many therapeutic interventions. Blunting sympathetic transmission with β adrenergic receptor antagonists is a cornerstone of therapy, prolonging life in patients who can tolerate β receptor blockade. Likewise, angiotensin converting enzyme inhibitors, angiotensin receptor 1 antagonists, and several other types of therapeutics decrease sympathetic nerve activity in humans with heart failure. Finally, exercise training is effective at both increasing cardiac vagal tone and decreasing sympathetic tone in patients who are able to undertake exercise. In addition to these proven treatments, several forms of neural modulation are under investigation to restore autonomic equilibrium including vagal nerve stimulation, electrical activation of the carotid baroreceptor reflex, destruction of afferent renal nerves, and device-based inhibition of carotid chemoreceptors (1).

A new study from Dyavanapalli et al. (2) in this issue of *JACC: Basic to Translational Science* identifies an intriguing new target for enhancing parasympathetic transmission during heart failure: oxytocin. Oxytocin (OXT) is a 9 amino acid peptide that is made in the hypothalamus and released into the circulation from the posterior pituitary. Its classic effects relate to social bonding, reproduction, and childbirth, but newer studies have identified roles for OXT neurotransmission within the central nervous system in regulating cardiovascular homeostasis, metabolic homeostasis, and bone density. OXT-producing neurons in the paraventricular nucleus (PVN) of the hypothalamus mediate these effects via projections throughout the brain stem, including the dorsal motor nucleus of the vagus, the nearby nucleus of the solitary tract, and multiple sympathetic targets including the intermediolateral cell column. With regard to cardiovascular homeostasis, distinct populations of OXT-releasing neurons stimulate parasympathetic transmission via the dorsal motor nucleus of the vagus (with possible involvement of the nucleus of the solitary tract), or they stimulate sympathetic outflow via the intermediolateral cell column and other targets (3). The study by Dyavanapalli et al. (2) builds on work showing that glutamatergic neurons in the PVN that coexpress the peptide OXT activate cardiac parasympathetic neurons in the dorsal motor nucleus of the vagus. Cardiac

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From the [a]Department of Chemical Physiology and Biochemistry, Oregon Health and Science University, Portland, Oregon; [b]Department of Anesthesiology and Perioperative Medicine, Oregon Health and Science University, Portland, Oregon; and the [c]Department of Medicine, Knight Cardiovascular Institute, Oregon Health and Science University, Portland, Oregon. Dr. Habecker has reported that she has no relationships relevant to the contents of this paper to disclose.

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vagal neurons are less active in heart failure, due in part to decreased excitatory glutamatergic inputs. The current study provides evidence that the release of OXT from PVN neurons onto cardiac vagal motor neurons decreases during heart failure and that chemogenetic activation of glutamatergic OXT neurons increases parasympathetic transmission and blunts the development of cardiac pathology.

The study began by asking the simple but technically daunting question "Does OXT release from hypothalamic PVN neurons onto cardiac vagal neurons decrease in heart failure?" There are no good methods to quantify synaptic peptide levels, so Dyavanapalli et al. (2) combined multiple methods to address this question. First, they selectively expressed channelrhodopsin-2 in PVN oxytocin neurons so that OXT release could be stimulated by light activation of channelrhodopsin-2. Then they added a "sniffer cell" bioassay to the dorsal motor nucleus region of their brain stem slice preparation, using cells engineered to link OXT receptor activation to the red fluorescent genetically encoded Ca^{2+} indicator R-GECO. This sensitive bioassay revealed that OXT release declined as heart failure developed in animals with transaortic constriction-induced pressure overload. A drawback of this method is the need to use a different set of sniffer cells for each time point, generating variability as each batch exhibits different levels of reporter expression and sensitivity. However, the general trend was clear that release of OXT was impaired in animals that developed heart failure compared with in sham animals, and the physiological changes were consistent across time.

Injecting OXT directly into the dorsal motor nucleus of the vagus triggers parasympathetic activation and bradycardia. The loss of OXT release onto those neurons during heart failure may therefore contribute to the loss of parasympathetic transmission. The investigators showed previously that expressing an excitatory chemogenetic receptor (designer receptor exclusively activated by designer drugs) in OXT neurons within the PVN could stimulate cardiac parasympathetic activity (4). Here they chronically activated excitatory DREADDs (designer receptor exclusively activated by designer drugs) in PVN OXT neurons with the ligand clozapine N-oxide beginning 4 or 6 weeks after pressure overload. They assessed cardiac and autonomic parameters in conscious animals throughout the 16-week study. Although the study did not measure vagal nerve activity, ongoing treatment with clozapine N-oxide lowered heart rate and improved heart rate return after exercise throughout the study duration, suggesting that cardiac parasympathetic tone was increased. In addition to enhancing parasympathetic transmission, the DREADD activation of hypothalamic OXT release decreased mortality, improved indices of cardiac function, and decreased cardiac fibrosis. Expression of inflammatory cytokines was also lowered, consistent with cholinergic suppression of cardiac inflammation in other contexts.

The translational potential of oxytocin use in humans makes this study especially intriguing. Although OXT can modulate both parasympathetic and sympathetic outflow from the central nervous system, systemic administration of OXT decreases heart rate, suggesting that the parasympathetic effects predominate. Indeed, intranasal administration of oxytocin in healthy humans increases parasympathetic and decreases sympathetic transmission to the heart (5). Oxytocin also increases cardiac parasympathetic drive in patients with obstructive sleep apnea. These human data and the new study from Dyavanapalli et al. (2) raise the possibility that intranasal OXT administration might be useful for increasing parasympathetic tone in heart failure.

The observation of deficient OXT release in the brain stem during heart failure is important, because replacing OXT back to a normal level may be less likely to cause unwanted side effects than adding excess OXT. In animal studies, the lack of OXT or its receptor leads to profound bone defects and late-onset obesity, and replacing OXT exogenously restores normal function. Similarly, OXT reverses ovariectomy-induced osteopenia and body fat gain in mice. In humans, the concentration of circulating OXT is positively associated with bone mineral density and lean mass, and heart failure patients are more likely than age-matched control subjects to have decreased bone mineral density and osteoporosis. Heart failure patients are also more likely to experience fractures even though many therapeutics used to treat heart failure decrease fracture risk (6). The observation of decreased OXT in this rat model of heart failure suggests a potential contributor to bone loss in humans with heart failure. Thus, boosting OXT levels in heart failure patients could potentially contribute to multiple beneficial outcomes, including enhanced parasympathetic transmission in the heart.

ADDRESS FOR CORRESPONDENCE: Dr. Beth A. Habecker, Department of Chemical Physiology and Biochemistry, Oregon Health and Science University, 3181 Southwest Sam Jackson Park Road, L334, Portland, Oregon 97239. E-mail: habecker@ohsu.edu.

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