Molecular mechanisms of dysautonomia during heart failure. Focus on “Heart failure-induced changes of voltage-gated Ca\(^{2+}\) channels and cell excitability in rat cardiac postganglionic neurons”

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HEART FAILURE IS A PROGRESSIVE syndrome primarily defined by the inability of the ventricles to fill or eject blood properly. However, the etiology and progression of this disease involve multiple organs and systems. One of the key contributors to worsening of heart failure with left ventricular systolic dysfunction is abnormal activity of the autonomic nervous system, whereby compensatory mechanisms designed to preserve cardiac output and organ perfusion accelerate deterioration of cardiac function. It has been observed that during heart failure there is sympathetic nervous system hyperactivity as evidenced by increased muscle sympathetic nerve activity and high rates of norepinephrine spillover (7). There also appears to be a concurrent impairment in vagus nerve activity, which is reflected in a decrease in heart rate variability (5). Both the enhanced sympathetic tone and reduced vagal outflow to the heart have been established as predictive of poor outcomes in heart failure (7).

Cardiac Autonomic Dysfunction During Heart Failure

The underlying molecular mechanisms involved in the altered autonomic imbalance during heart failure remain poorly understood. Autonomic control of cardiac function involves a hierarchy of peripheral autonomic neurons that are influenced by central projections and depend on feedback from sensory neurons at the level of the ganglion, spinal cord, and central nervous system (Fig. 1) (1). The cardiac autonomic imbalance observed during heart failure may be due to changes occurring in any of these nested loops or due to alterations in the capacity of the heart to respond to autonomic input. Previous studies suggested that the reduction in response to parasympathetic activation is not due to end-organ receptor downregulation or signaling dysfunction, since there is an increase in M2 muscarinic responses in the heart (11). Similarly, direct stimulation of post-ganglionic parasympathetic neurons could elicit the predicted changes to cardiac parameters, indicating that these neurons had the capacity to release normal amounts of acetylcholine (3). Several studies, however, pointed to dysfunction at the level of the intrinsic cardiac ganglion during heart failure, but the mechanism remained unclear (2, 3). To date, an important question remained to be answered, “Is there a reduction in vagal input to the ganglion or is the activity of parasympathetic intrinsic cardiac neurons depressed following heart failure?”

The molecular remodeling that occurs in the sympathetic nervous system is also poorly understood. Sympathetic dysfunction appears to be in part due to depressed expression of \(\beta_1\)-adrenergic receptors and disruption of the normal signaling and regulation of these receptors on the heart (7). However, there also appears to be sympathetic nervous system remodeling after heart failure. For example, heart failure induces enhanced activity of the stellate ganglion and this hyperactivity is associated with an increased incidence of arrhythmias (6). Paradoxically, there are also data suggesting that after heart failure there is a reduction in norepinephrine release from stellate ganglion neurons (4). As with the parasympathetic branch, the specific level in the network and the precise molecular mechanisms producing the heart failure-associated changes in sympathetic tone remain to be fully elucidated.

N-Type Calcium Channels and Heart Failure-Induced Dysautonomia

In this issue of American Journal of Physiology-Cell Physiology, Tu et al. (10) identify a specific molecule that may be involved in both the hyperactivity of the sympathetic nervous system and the blunting of parasympathetic tone following myocardial infarction-evoked heart failure in rats. The expression of several voltage-activated calcium channel (VACC) \(\alpha\)-subunits was examined both in efferent cardiac postganglionic parasympathetic (CPP) neurons from intrinsic cardiac ganglia and in efferent cardiac postganglionic sympathetic (CPS) neurons from stellate ganglia in rats under normal conditions and following heart failure. Heart failure only altered the expression of N-type calcium channel (Cav2.2), with both the amount of mRNA and protein for this VACC subtype being reduced exclusively in CPP neurons. The reduction in Cav2.2 resulted in functional downregulation of currents through these channels in CPP neurons and was accompanied by a decrease in the excitability of these cells. Importantly, this reduction in neuroexcitability could be mimicked by exposing CPP neurons to the N-type VACC inhibitor \(\omega\)-conotoxin. While expression of N-type VACC was not altered in CPS neurons following heart failure, there was an observed enhancement of N-type VACC-mediated currents in CPS neurons and a concomitant enhancement of neuroexcitability. Blocking the N-type VACC with \(\omega\)-conotoxin in CPS neurons from heart failure animals reduces neuroexcitability.

The findings reported by Tu et al. (10) are particularly significant for several reasons. First, this report identifies for the first time a specific protein that is altered by heart failure at the level of cardiac autonomic ganglia. Second, the functional upregulation and downregulation of this protein in the sympathetic and parasympathetic cardiac neurons, respectively, and the associated changes in neuroexcitability, directly correlate with the known changes in autonomic input to the heart following heart failure. Thus, changes in Cav2.2 may account,
Fig. 1. Hierarchical model for organization of autonomic innervation of the heart. Model shows the different structural layers involved in autonomic control of the heart. Intrinsic cardiac neurons mediate all parasympathetic input to the heart. Sympathetic innervation is primarily provided via neurons located in intrathoracic extracardiac ganglia (stellate, middle cervical, superior cervical, and mediastinal ganglia), with a smaller population of sympathetic, adrenergic neurons within the intracardiac ganglion. Chemosensory and mechanosensory feedback to the central nervous system (CNS) is provided byafferent neurons with somata located within the nodose and dorsal root ganglia. Other sensory elements, however, can be found within the intracardiac and intrathoracic extracardiac ganglia, and provide direct feedback at these sites. Findings reported by Tu et al. (10) indicate that efferent postganglionic sympathetic (CPS) neurons have enhanced activity, whereas efferent postganglionic parasympathetic (CPP) neurons have depressed excitability, following heart failure. [Adapted from Armour (1), with permission.]

in part, for the observed heart failure-evoked dysautonomia. Finally, the fact that inhibition of this channel can mimic the effects of heart failure in CPP neurons from control animals (i.e., depress their excitability) and reverse the augmented excitability of CPS neurons in heart failure animals suggests that Cav2.2 may be a potential target for reversing some of the dysfunction of the autonomic nervous system caused by heart failure.

Future Directions

The role of Cav2.2 in the etiology of heart failure-induced autonomic dysfunction remains to be fully explored. The Tu et al. (10) study clearly shows that CPP neurons have depressed expression of Cav2.2. However, it is unknown if similar changes occur in local circuit neurons of the intrinsic cardiac ganglion (Fig. 1). These neurons play a critical role in processing of information within the ganglia and facilitate cross talk between parasympathetic and sympathetic components of the ganglia. Likewise, questions remain regarding the governing mechanism(s) resulting in the functional upregulation of N-type VACC in CPS neurons in the absence of elevations in protein expression. For example, are there changes to auxiliary subunits associated with Cav2.2, and can these changes account for the increases in current amplitude? Finally, it is important to note that N-type VACC are known to regulate neurotransmitter release, and thus these changes in N-type channel function may have a direct impact on the release of acetylcholine and norepinephrine in addition to altering neuroexcitability (8). Such possible changes in neurotransmitter release produced by alterations in Cav2.2 need to be examined.

REFERENCES