Enhanced astroglial GABA uptake in heart failure

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Chronic heart failure is characterized by exaggerated sympathoexcitation in both human patients and animal models. Despite major advances in therapy, the increased neurohumoral drive causes significant cardiovascular complications that contribute to increased morbidity and mortality. Blunted GABAergic inhibition in the hypothalamic paraventricular nucleus (PVN) has been suggested as a key integrating mechanism of the sympathoexcitation associated with cardiovascular-related disorders such as hypertension, diabetes, and heart failure. The GABA$_A$ receptor (GABA$_A$R), a pentameric ligand-gated Cl$^-$ channel, mediates 2 inhibitory modalities in the PVN: a conventional inhibitory synaptic current (IPSC) mediated by synaptic GABA$_A$R$_{gs}$, and a persistent tonic inhibitory current (termed $I_{\text{tonic}}$) generated by extrasynaptic GABA$_A$R$_{gs}$. As in other brain regions, $I_{\text{tonic}}$ mediates the dominant portion of GABA$_A$R-mediated inhibition and thus has a major impact on PVN neurons projecting to the rostral ventrolateral medulla (PVN-RVLM) neuronal excitability. However, the pathophysiological significance of $I_{\text{tonic}}$ in sympathoexcitation remains poorly understood. In a recent study using brain slice patch-clamping, Sudip and colleagues showed that $I_{\text{tonic}}$, defined as the holding current shift by the GABA$_A$R antagonist bicuculline, was attenuated in the PVN-RVLM in rats with myocardial infarction (MI)-induced heart failure (HF). The authors suggested that this deficit in GABAergic tonic inhibition of the pre-sympathetic neurons and the resulting increased sympathetic output from the PVN during HF is attributable to enhanced astroglial GABA uptake.

$I_{\text{tonic}}$ generated by activation of extrasynaptic GABA$_A$R$_{gs}$ is tightly controlled by extracellular GABA concentration as well as the expression and combination of extrasynaptic GABA$_A$R$_{gs}$ in specific brain regions. In addition to vesicular GABA release, $I_{\text{tonic}}$ is also generated by extrasynaptic GABA$_A$R$_{gs}$ in specific brain regions. Given that $I_{\text{tonic}}$ amplitude correlates with vesicular GABA release, HF $I_{\text{tonic}}$ attenuation may result from reduced ambient GABA concentrations related to a decrease in IPSC frequency in HF PVN-RVLM neurons. Collectively, the finding that GAT blockers mask and reverse HF $I_{\text{tonic}}$ attenuation suggests that blockade of enhanced GAT activity could compensate and even overpower impaired vesicular GABA release in HF PVN-RVLM neurons. Using pharmacological probes, Sudip and colleagues also investigated possible changes in extrasynaptic GABA$_A$R function in HF. Reduced $I_{\text{tonic}}$ sensitivity to THIP (4,5,6,7-tetrahydroisothiazolo-[5,4-c]pyridin-3-ol) supported decreased function of GABA$_A$R $\delta$ subunits in HF, whereas similar $I_{\text{tonic}}$ sensitivity to benzodiazepines indicated that $\gamma_2$ subunit-containing GABA$_A$R$_{gs}$ do not differ between sham-operated and post-MI rats. Thus, despite reduced GABA$_A$R $\delta$ subunit function, the increased impact on GABA$_A$R $\gamma_2$ subunits mediating $I_{\text{tonic}}$ may enable GAT blockade to reverse...
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onic attenuation in HF PVN-RVLM neurons.

Sudip et al. found that I

onic attenuation increased membrane input resistance (IR) and firing discharge rate in HF PVN-RVLM neurons, indicating that I

onic, as the dominant portion of GABAAR-mediated inhibition, has a major impact on PVN-RVLM neuronal excitability. 1 The direct impact of I

onic on membrane IR, and thus the membrane time constant, may affect synaptic efficacy and integration in neurons. Accordingly, Sudip and colleagues observed a leftward shift in the input-output (I-O) function of HF PVN-RVLM neurons, reversed by NPA, suggesting that I

onic attenuation significantly impacts neuronal sensitivity to incoming excitatory and/or inhibitory synaptic inputs in the HF PVN-RVLM. Therefore, the increased impact on membrane IR and the I-O function would enable GAT blockade to correct the altered synaptic efficacy and integration in HF PVN-RVLM neurons. This conclusion is further supported by the finding that NPA efficiently inhibits the increased spontaneous firing in HF PVN-RVLM neurons.

In conclusion, Sudip and colleagues showed that enhanced astroglial GABA uptake attenuates I

onic and, in turn, increases neuronal firing of pre-sympathetic PVN neurons in heart failure. The data demonstrate a link between pathophysiology and GAT-3 uptake modulation of GABA

R tonic inhibition in the brain during altered autonomic nerve activity and highlight the potential of targeting astroglial GABA clearance to reduce sympathoexcitation associated with cardiovascular disorders.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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Figure 1. Regulation of GABA

R tonic inhibition of the pre-sympathetic PVN neurons in normal rats and following heart failure. Combined with decreased vesicular GABA release (A) and reduced function of extrasynaptic GABA

R containing δ subunits (B), enhanced astroglial GABA clearance via GAT-3 (C) attenuates GABA

R tonic inhibition and increases neuronal firing in heart failure.