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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 ($GABA_AR$), a pentameric ligand-gated Cl^- channel, mediates 2 inhibitory modalities in the PVN: a conventional inhibitory synaptic current (IPSC) mediated by synaptic $GABA_ARs$, and a persistent tonic inhibitory current (termed I_{tonic}) generated by extrasynaptic $GABA_ARs$. As in other brain regions, I_{tonic} mediates the dominant portion of $GABA_AR$-mediated inhibition and thus has a major impact on PVN neurons projecting to the rostral ventrolateral medulla (PVN-RVLM) neuronal excitability.[1] However, the pathophysiological significance of I_{tonic} in sympathoexcitation remains poorly understood. In a recent study using brain slice patch-clamping,[2] Sudip and colleagues showed that I_{tonic}, defined as the holding current shift by the $GABA_AR$ 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 outflow from the PVN during HF is attributable to enhanced astroglial GABA uptake.

I_{tonic} generated by activation of extrasynaptic $GABA_ARs$ is tightly controlled by extracellular GABA concentration as well as the expression and combination of extrasynaptic $GABA_ARs$ in specific brain regions. In addition to vesicular GABA release responsible for activating IPSCs,[1,3] GABA released from glia contributes to I_{tonic} generation in the brain. GABA transporter (GAT) reversal has been suggested in pathological conditions, while a debated role for the GABA-releasing anion channel bestrophin-1 (Best-1) has been proposed to explain physiological and pathophysiological GABA release from glia. Despite evidence for GAT reversal under pathophysiological conditions, GATs are generally believed to uptake extracellular GABA into cells. Of the 4 GATs (GAT-1, GAT-2, GAT-3, and BGT-1), GAT-1 and GAT-3 are most likely to be expressed in neurons and glia, respectively, and to be responsible for ambient GABA levels in the brain (**Fig. 1**).[4] Pharmacological or genetic inhibition of GAT-1 increases I_{tonic}, which is associated with neurological and psychological disorders. However, the relationship between astroglial GABA clearance by GAT-3 and its effects on I_{tonic} modulation and neuronal activity under pathological conditions are poorly understood. Sudip and colleagues showed that HF I_{tonic} attenuation was reversed by a nonselective GAT blocker (nipecotic acid, NPA) and a GAT-3 selective blocker (SNAP-5114), but not by a GAT-1 blocker (NO-711), suggesting that astroglial GABA uptake plays a major role in I_{tonic} regulation of HF in PVN-RVLM neurons,[2] as in the naïve PVN.[5] To exclude the involvement of BEST-1-mediated GABA release in HF I_{tonic} attenuation, Sudip et al. showed that BEST-1 blockade did not affect I_{tonic} in either sham-operated or post-MI rats.

Given that I_{tonic} amplitude correlates with vesicular GABA release, HF I_{tonic} attenuation may result from reduced ambient GABA concentrations related to a decrease in IPSC frequency in HF PVN-RVLM neurons.[6] Collectively, the finding that GAT blockers mask and reverse HF I_{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 $GABA_AR$ function in HF. Reduced I_{tonic} sensitivity to THIP (4,5,6,7-tetrahydroisothiazolo-[5,4-c]pyridin-3-ol) supported decreased function of $GABA_AR$ δ subunits in HF, whereas similar I_{tonic} sensitivity to benzodiazepines indicated that γ_2 subunit-containing $GABA_ARs$ do not differ between sham-operated and post-MI rats. Thus, despite reduced $GABA_AR$ δ subunit function, the increased impact on $GABA_AR$ γ_2 subunits mediating I_{tonic} may enable GAT blockade to reverse

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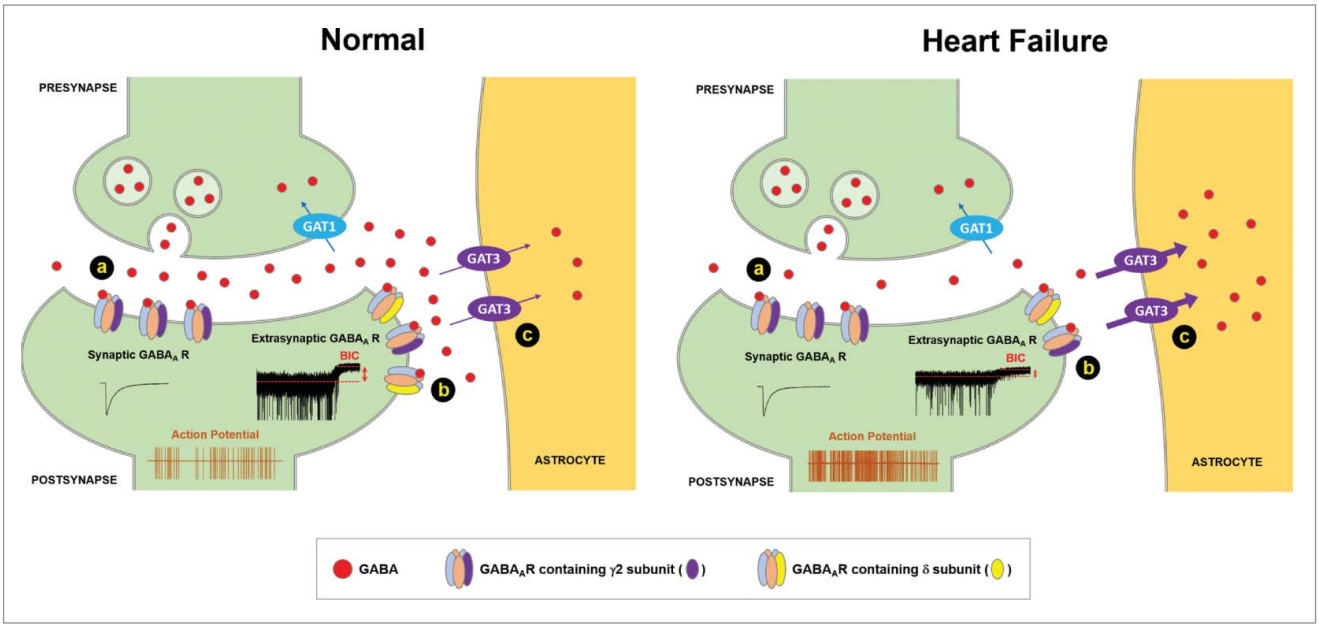

Figure 1. Regulation of $GABA_A$ tonic inhibition of the pre-sympathetic PVN neurons in normal rats and following heart failure. Combined with decreased vesicular GABA release (**A**) and reduced function of extrasynaptic $GABA_A$Rs containing δ subunits (**B**), enhanced astroglial GABA clearance via GAT-3 (**C**) attenuates $GABA_A$ tonic inhibition and increases neuronal firing in heart failure.

I_{tonic} attenuation in HF PVN-RVLM neurons.

Sudip et al. found that I_{tonic} attenuation increased membrane input resistance (IR) and firing discharge rate in HF PVN-RVLM neurons, indicating that I_{tonic}, as the dominant portion of $GABA_A$R-mediated inhibition, has a major impact on PVN-RVLM neuronal excitability.[1] The direct impact of I_{tonic} on membrane IR, and thus the membrane time constant, may affect synaptic efficacy and integration in neurons.[7] 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_{tonic} 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_{tonic} 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 $GABA_A$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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