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EDITORIAL COMMENT

Cardioprotective role of GABA-B receptor activation on ventricular arrhythmia following myocardial infarction

O papel cardioprotetor da ativação do recetor GABA-B nas arritmias ventriculares após enfarte do miocárdio

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Fatal ventricular arrhythmias (VAs) are the leading cause of sudden cardiac death among patients surviving a myocardial infarction (MI).[1] Multiple mechanisms are involved in the development of VAs after MI, including remodeling of ion channels, gap junctions, and histological changes. Sympathetic nerve hyperactivity has also been proposed as a major contributing factor.[2,3] In fact, although rapid activation of the sympathetic nervous system after MI is an important compensatory mechanism for impaired myocardial function, it has been also implicated in increased local norepinephrine (NE) release, triggering malignant arrhythmias.[3] Furthermore, resident and recruited immune cells following MI were shown to elicit a massive inflammatory response that can induce sympathetic remodeling.[4] Hence, it is proposed that macrophages play a key role in this mechanism, arising as a valuable therapeutic target against VAs.

Multiple neurotransmitters are known to control sympathetic nerve activity, and consequently, cardiovascular function. Interestingly, both glutamate (excitatory) and gamma-aminobutyric acid (GABA; inhibitory) were reported to regulate susceptibility to arrhythmia in hypertensive rats.[5] Nonetheless, the mechanisms underlying such responses remain largely unexplored. In recent years, it was uncovered that peripheral immune cells and microglia express GABA receptors subtypes A and B (GABA-A and GABA-B).[6] Therefore, it is conceivable that GABAergic signaling in cardiac resident immune cells modulate sympathetic activity, including under pathological conditions.

This is the question addressed by Qian Liu et al.[7] in the manuscript ''The protective effect of GABAB receptor activation on sympathetic nerve remodeling via regulating M2 macrophage polarization after myocardial infarction''. In this article, the authors report the expression of the GABA-B receptor in cultured macrophages, as well as in CD206-positive cells in rat hearts. Moreover, the authors demonstrate GABA-B activation in vitro, either by GABA or with the selective agonist baclofen, promotes the expression of CD206, suggesting a role for GABA-B in mediating transition into alternatively activated macrophages (also termed M2 macrophages). Importantly, they show a similar

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increased number of alternatively activated macrophages following baclofen treatment in an animal model of MI, with a concomitant decrease in serum-circulating pro-inflammatory cytokines.

Modulation of GABAergic signaling at the onset of MI is not without precedents. In fact, the GABA-A agonist topiramate was previously demonstrated to modulate macrophage phenotype conversion towards the M2/Ly-6C^{low} phenotype, being associated with decreased inflammation, reduced infarct size and improved cardiac function after MI.[8] In contrast, data gathered here show that treatment with baclofen did not significantly reduce infarct size, nor increased survival of mice post-MI. Nonetheless, a protective effect was observed by in vivo administration of GABA, suggesting that the role of GABA-A receptors prevail over GABA-B in controlling post-infarction ventricular remodeling. Besides their immunomodulatory roles, molecules secreted by macrophages can directly impact cardiac electric impulse propagation and modulate arrhythmogenesis. Indeed, it was recently demonstrated that amphiregulin produced by cardiac macrophages prevents the lateralization of the gap junctional protein Connexin43 (Cx43) in cardiomyocytes, which may be relevant in suppressing arrhythmia following MI.[9,10] Therefore, further investigation should aim at a better understanding of the contribution of macrophage polarization and secretome to arrhythmogenesis and structural remodeling of the heart.

Qian Liu et al. also addressed the impact of GABA-B activation in sympathetic nerve remodeling and demonstrate that baclofen counteracted the accumulation of tyrosine hydroxylase (TH) and growth-associated protein 43 (GAP 43) in infarcted hearts. This was accompanied by decreased serum levels of NE, suggesting that baclofen can prevent sympathetic nerve sprouting and activity in vivo. Although arrhythmogenesis after MI was still observed in animals treated with GABA, it is still conceivable that the frequency and/or duration of those arrhythmic phenomena would be decreased, thereby explaining the higher survival rates of treated animals.

Nonetheless, future studies are required to characterize, in-depth, the role of GABAergic signaling in the development of fatal VAs, as well as to establish novel therapies. Comprehensive strategies targeting not only GABA receptors, but also macrophage polarization and communication networks comprising cardiomyocytes and sympathetic neurons, will be key to the prevention of sudden death following MI.[2]

Conflicts of interest

The author has no conflicts of interest to declare.

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