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Editorial

Neuroinflammation as a mechanism for cardiovascular diseases

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The stellate ganglia (SG) are the main source of sympathetic innervation to the heart and undergo remodeling in cardiovascular diseases, thereby contributing to disease progression [1]. Following myocardial infarction (MI), neurons within the SG undergo changes in morphology and phenotype [2,3] as well as alterations in their behavior [4]. Structurally, SG neurons enlarge after MI [2] and undergo adrenergic-to-cholinergic transdifferentiation in heart failure [3]. Functionally, hyperactivity of the SG has been shown to precede the onset of ventricular arrhythmias following MI [4]. At the level of the heart, there are also changes in sympathetic innervation [5] and of sympathetic control of electrophysiology [6]. The remodeling of the SG, along with other neuronal populations within the autonomic nervous system (ANS) [7], plays a major role in the pathophysiology of cardiovascular diseases including arrhythmias and heart failure [1]. Thus, the SG have become an important therapeutic target. Unilateral left cardiac sympathetic denervation, for example, is an established, effective procedure to prevent life-threatening ventricular arrhythmias in patients with channelopathies [8,9], and bilateral cardiac sympathetic denervation has emerged as a promising treatment for patients with refractory ventricular arrhythmias [10].

The mechanisms underlying the neuronal remodeling that occurs with cardiovascular diseases are not well understood and are multifactorial including changes in afferent signaling, disruptions in cardiac reflexes, and inflammation. The link between inflammation and alterations in neural function in the central and peripheral nervous system is now well recognized. Cytokines released during inflammatory processes have been shown to have neuromodulatory effects. Proinflammatory cytokines such as interleukin (IL)-1β, tumor necrosis factor-α (TNF-α), and IL-6 can affect the production and metabolism of neurotransmitters [11]. They can also modulate the behavior and distribution of ion channels to affect synaptic transmission and plasticity [12]. In addition, these cytokines can cause activation of glial cells [12]. In the brain, these inflammation-mediated changes can lead to neuronal dysfunction and hyperexcitability and, ultimately, neuropathology (e.g., epilepsy, seizures) [12]. Neuroinflammation also plays an important role in diseases outside the brain including those of the heart. In 1979, a case report described cardiac ganglionitis in two patients that died from sudden cardiac arrest [13]. SG from patients with long QT syndrome and catecholaminergic polymorphic ventricular tachycardia have been shown to have the presence of T lymphocytes and macrophages [14]. A recent study by Ajijola and colleagues also found that in SG from cardiomyopathy patients there was infiltration of inflammatory cells, evidence of oxidative stress, and satellite glial cell activation [15]. Clinically, patients with ongoing inflammatory processes (e.g., post-surgery, myocarditis, rheumatoid arthritis) are known to be at an increased risk for arrhythmias [16,17]. Furthermore, the relationship between inflammation and the nervous system remains a largely underexplored area in the pathophysiology of cardiovascular diseases, which could lead to novel treatments.

In this issue of *International Journal of Cardiology*, Deng and colleagues investigated the acute effects of the proinflammatory cytokine IL-17A on the SG and ventricular electrophysiology in a canine model. The authors demonstrated that injection of IL-17A into the left stellate ganglion (LSG) upregulated the expression of: 1) other proinflammatory cytokines (TNF-α, IL-6, IL-1β); 2) p-TrkA, the activated receptor for nerve growth factor; and 3) c-Fos, an immediate early gene that is rapidly activated in response to a wide variety of cellular stimuli, in the LSG. The in vivo activity of the LSG was also enhanced. In the heart, there was an increase in dispersion of the ventricular effective refractory period, the action potential duration (APD) at 90% repolarization, and APD alternans cycle length. All of these changes were attenuated by the co-injection of an anti-IL-17A monoclonal antibody. A prior study from the same group showed that IL-1β had similar effects as IL-17A on the LSG and destabilized ventricular electrophysiology, increasing the incidence of myocardial ischemia-induced ventricular arrhythmias [18]. Taken together, these data from structurally normal and diseased hearts provide compelling evidence for a link between neuroinflammation and alterations in cardiac function.

Although these findings are intriguing, there are some limitations. In this present study, a single proinflammatory cytokine—IL-17A—was injected directly into the LSG. However, inflammation is characterized by a complex interplay between numerous pro- and anti-inflammatory cytokines [19]. In inflammatory states such as MI, cytokines also circulate systemically and likely modulate neurons within the ANS, both peripherally and centrally [12]. Studying the effects of an exogenously administered cytokine on one part of the ANS in isolation is too simplistic. In addition, the acute nature of these studies makes it challenging to place the results in the context of a subacute or chronic inflammatory disease process such as MI. Furthermore, electrophysiological indices were used as a surrogate for arrhythmogenicity in this model rather than directly testing ventricular tachycardia inducibility or showing the incidence of

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spontaneous ventricular tachycardia or ventricular fibrillation. To improve the translational potential, future studies should investigate whether there are alterations in neuronal, cardiac function, and arrhythmogenicity in response to MI-induced inflammation and then evaluate whether localized or systemic anti-inflammatory therapy attenuates these effects. The findings of this study underscore the importance of better understanding the relationship between neuroinflammation and cardiac disease.

Conflict of interest

The authors report no relationships that could be construed as a conflict of interest.

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