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Nerve Growth Factor Mediates the Vious Cycle between Hyperactivity of Ganglionated Plexus and Atrial Fibrillation

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Abstract

Ganglionated Plexus (GP) is a complex neural network composed by intrinsic cardiac autonomic nervous system (ANS) and is mainly located in fat pads around the antrum of the pulmonary veins (PVs). Recent studies demonstrated hyperactivity of GPs and atrial fbrillation (AF) formed a vicious cycle, to be specifc, hyperactivity of the cardiac GPs facilitated the initiation and maintenance of AF and the activity of cardiac GPs increased as AF continued. In addition, research has confrmed that the Nav1.8 channel is highly expressed in GPs and is closely related to activity of GPs and the inducibility of AF. Nerve growth factor (NGF) is an important neurotrophic factor and the expression of NGF in GPs is up-regulated during AF over time, which could trigger the release of SP in the heart *via* TRPV1 signaling pathways. Besides, SP could rapidly increase the activity of the Nav1.8 channel, demonstrating the increment of Sensory nerve action potentials. Therefore, we hypothesized that up-regulated NGF during AF could increase the activity of GPs through TRPV1-SP-Nav1.8 channel pathways and contributes to stability of AF. If this hypothesis is proved to be correct, future studies based on this link may help to fnd new therapeutic targets for the treatment of AF.

Keywords: Ganglionated Plexus; Atrial brillation; Nerve growth factor; Nav1.8 channel; TRPV1 receptor

Short Communication

Atrial brillation (AF) is the most common cardiac arrhythmia, and the prevalence of AF is expected to increase dramatically over the next few decades [1]. Although AF itself is not typically lethal, it is associated with an increased risk of stroke, heart failure, and dementia, as well as cardiovascular-related and all-cause mortality [2]. In addition, AF accounts for more than one-third of all arrhythmia-related hospitali ations [3]. Once AF is initiated, it is inclined to sustain itself and cause changes in progressive electrical remodeling [4] and structural remodeling [5] of the atria and that promote the occurrence and maintenance of AF, knowing as the concept of ¸AF begets AF–. Recent years, emerging evidence indicated that autonomic remodeling has a close link with the initiation and maintenance of AF [6].

The Relationship between Atrial Neural Hyperactivity and AF Inducibility

Cardiac autonomic nerve is made up of two main components: the extrinsic and intrinsic autonomic nervous system (ANS). e former consists mainly of ganglia and their axons located outside the heart and the latter is composed mainly of ganglionated plexi and their axons, which are typically embedded in the epicardial fat pads [7]. As to human hearts, there are at least 7 GP and 4 major le atrial GP are located around the antrum of the PVs [8]. In addition, most of intrinsic cardiac neurons in GPs were found to be cholinergic.

Recently, Several lines of evidence suggested that autonomic remodeling plays an important role in the pathogenesis of AF, which mainly demonstrated as the hyperactivity of the cardiac autonomic nervous system (ANS) [6,9,10] and sympathetic hyperinnervation [11] and changes of several protein such as nerve growth factor (NGF), small conductance calcium-activated potassium channel type 2 (SK2), neurturin (NRTN) [12,13], to be speci c, researchers found that both of extrinsic cardiac nerve activity (ECNA) and intrinsic cardiac nerve activity (ICNA) increased as AF continued. Moreover, in a canine model, researchers found that Stimulation of either the Aortic Root GP or anterior right ganglionated plexuses (GP) could trigger the initiation of AF [14,15]. On the contrary, several studies found that 1) destruction of epicardial fat pads by radiofrequency ablation or surgical excision [16,17], 2) blockade of autonomic nerve within GPs could induced a progressive increase in the AF threshold and prevented the initiation and maintenance of AF [18]. Taken together, these facts con rmed that hyperactivity of the cardiac ANS and AF formed a vicious cycle and suppressed the activity of GPs could e ective inhibit the inducibility of AF.

The Expression of NGF within Gps Up-Regulated as AF Continued

NGF is one of the most extensively studied neurotrophic factors, which can be synthesi ed by several types of cells, including lymphocytes, broblasts, macrophages and mast cells [19], and it is vital for the survival, di erentiation, and synaptic activity of the sympathetic and sensory nervous systems [20,21]. ere is considerable evidence that the expression of NGF became increasingly up-regulated throughout the progress of AF [12,13], high-frequency electrical eld stimulation (HFES) of both parasympathetic [22] and sympatheticneurons *in vitro* to mimic rapid atrial depolari ation further indicated that the cardiac autonomic neurons are an important source of NGF. Besides, abundant studies have shown that NGF plays an essential role in hyperalgesia and in¸ammatory pain [23], which are mainly associated with Nav1.8 channels [24] and TRPV1 receptors [25]. To be speci c, acute exposure of NGF can enhance the activity of TRPV1 receptor within half an hour through phosphoinositide-3-kinase and mitogen activated protein kinase signaling pathways [26] and subsequently trigger the

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