Modulation of Cardiac Potassium Current by Neural Tone and Ischemia

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KEYWORDS

• Autonomic nervous system • Cardiac arrhythmias • Potassium channels
• Acetylcholine-activated potassium channel • ATP-sensitive potassium channel • Atrial fibrillation

KEY POINTS

- Modulation of the flow of potassium across myocyte cell membranes results in changes to the cardiac action potential, and abnormalities of potassium current can result cardiac arrhythmias.
- The autonomic nervous system (ANS) has a role in regulation of cardiac potassium currents, and abnormalities in autonomic regulation of cardiac potassium currents can result in arrhythmias, including atrial fibrillation (AF), that may result from abnormal modulation of acetylcholine (ACh)-activated potassium channels.
- Ischemia is another important modulator of cardiac cellular electrophysiology that alters cardiac potassium current through effects on ATP-sensitive potassium channels in ways that may result in cardiac arrhythmias, in particular ventricular fibrillation.

INTRODUCTION

The cardiac action potential is generated by intricate flows of ions across myocyte cell membranes in a coordinated fashion that ultimately results in myocyte depolarization and then repolarization, which on a myocardial tissue level coordinates myocardial contraction and the heart rhythm. Modulation of the flow of these ions (primarily sodium, calcium, and potassium) in response to a variety of stimuli results in changes to the action potential. Although inward sodium and calcium currents are primarily responsible for the depolarization and plateau phases of the cardiac action potential, potassium currents contribute to the plateau phase but are primarily responsible for the repolarization phase of the cardiac action potential. Modulation of the potassium current results in alterations in cardiac action potential duration and repolarization, and abnormalities of the potassium current can result in cardiac arrhythmias. The ANS plays an important role in the modulation of cardiac electrophysiology as a whole and has a particularly important role in modulation of the potassium current in particular. The role of the ANS in modulation of the cardiac potassium current is discussed in this review. In addition, the effect of ischemia, another modulator of cardiac cellular electrophysiology, on potassium current is also discussed.

OVERVIEW OF THE CARDIAC AUTONOMIC NERVOUS SYSTEM

The heart is richly innervated by autonomic nerves. A general understanding of the anatomy of the cardiac ANS is useful in understanding the effects of the autonomic system in normal and diseased states. The cardiac ANS can be divided into extrinsic and intrinsic systems, with the extrinsic

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ANS comprising nerves outside the heart and the intrinsic ANS made up of nerves and ganglia within the pericardium and on the epicardial surface[1,2] (Fig. 1).

The extrinsic cardiac ANS consists of sympathetic and parasympathetic nerves. Preganglionic sympathetic neurons originate in the spinal cord and travel to the prevertebral autonomic ganglia, including the superior cervical ganglia, the stellate ganglia, and the thoracic ganglia.[3,4] The cell bodies of the postganglionic sympathetic neurons reside in these ganglia, and postganglionic sympathetic neurons travel from these ganglia to innervate both the atrial and ventricular surfaces of the heart via the superior, middle, and inferior cardiac nerves. Preganglionic parasympathetic neurons originate in the medulla oblongata. Parasympathetic neurons travel to the heart in the vagus nerve where they terminate primarily in fats pads in the atria and superior vena cava.

The intrinsic cardiac ANS consists of sympathetic and parasympathetic neurons after they enter the pericardial sac.[5] After entering the pericardial sac, sympathetic neurons either directly innervate the myocardium or form synapses within cardiac ganglia. All parasympathetic fibers, in contrast, form synapses within the cardiac ganglia. They are concentrated within the fat pads on the epicardial surface of the atria and ventricle and generally form groups of ganglionated plexi. Within the atria, the ganglionated plexi have been located in several areas, including the superior right atrium, the posterior right atrium, the superior left atrium (LA), the posteromedial LA, and the inferolateral LA, and they have been noted to be close to the PV ostia. Ventricular ganglionated plexi primarily localize to fat pads around the aortic root and the origins of the major coronary arteries.

CELLULAR MECHANISMS OF CARDIAC AUTONOMIC SIGNALING

Several reviews have discussed the cellular mechanisms of autonomic signaling in detail and are summarized in brief.[6–8] In response to stimulation, postganglionic sympathetic neurons release norepinephrine, which exerts its effects on cardiac myocytes primarily by activating β-receptors on the myocyte cell surface. β-Receptors are one of the numerous types of 7 transmembrane domain G protein–coupled receptors. Three subtypes of β-receptors exist, with the β_1-receptors the most common on cardiac cells, accounting for approximately 80% of cardiac β-receptors.[7] The G protein–coupled receptors are associated with G proteins that consist of 3 subunits, Gα, Gβ, and Gγ. When simulated by norepinephrine, the β_1-receptor triggers conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) on the Gα subunit of the G protein, causing Gα to dissociate from Gβ and Gγ. The primary Gα subunit associated with β-receptors is the stimulatory $G\alpha_s$ subunit. The dissociated $G\alpha_s$ subunit is then free to activate adenylyl cyclase, which converts ATP to cyclic adenosine monophosphate

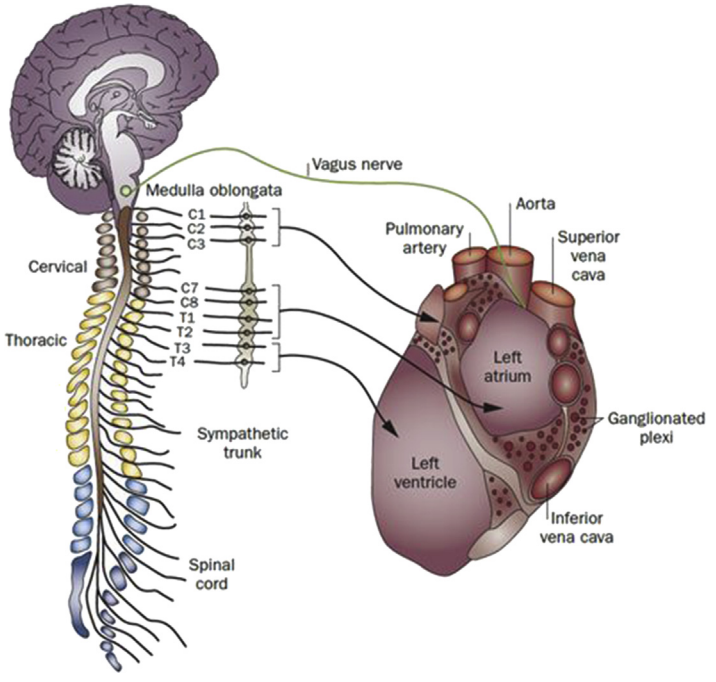

Fig. 1. Autonomic innervations of the heart. The extrinsic ANS comprises nerves outside the heart. The sympathetic ganglia include the cervical ganglia, the stellate ganglia, and the thoracic ganglia. The parasympathetic innervations of the heart arises from the vagus nerve. The intrinsic ANS is made up of nerves and ganglionated plexi within the pericardium and on the epicardial surface of the heart. (*From* Shen MJ, Choi EK, Tan AY, et al. Neural mechanisms of atrial arrhythmias. Nat Rev Cardiol 2011;9:30–9; with permission.)