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The role of the autonomic nervous system in arrhythmias and sudden cardiac death

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ABSTRACT

The autonomic nervous system (ANS) is complex and plays an important role in cardiac arrhythmia pathogenesis. A deeper understanding of the anatomy and development of the ANS has shed light on its involvement in cardiac arrhythmias. Alterations in levels of Sema-3a and NGF, both growth factors involved in innervation patterning during development of the ANS, leads to cardiac arrhythmias. Dysregulation of the ANS, including polymorphisms in genes involved in ANS development, have been implicated in sudden infant death syndrome. Disruptions in the sympathetic and/or parasympathetic systems of the ANS can lead to cardiac arrhythmias and can vary depending on the type of arrhythmia. Simultaneous stimulation of both the sympathetic and parasympathetic systems is thought to lead to atrial fibrillation whereas increased sympathetic stimulation is thought to lead to ventricular fibrillation or ventricular tachycardia. In inherited arrhythmia syndromes, such as Long QT and Catecholaminergic Polymorphic Ventricular Tachycardia, sympathetic system stimulation is thought to lead to ventricular tachycardia, subsequent arrhythmias, and in severe cases, cardiac death. On the other hand, arrhythmic events in Brugada Syndrome have been associated with periods of high parasympathetic tone. Increasing evidence suggests that modulation of the ANS as a therapeutic strategy in the treatment of cardiac arrhythmias is safe and effective. Further studies investigating the involvement of the ANS in arrhythmia pathogenesis and its modulation for the treatment of cardiac arrhythmias is warranted.

1. Overview of the cardiac nervous system

Death due to cardiac arrhythmias remains a significant problem of epidemic proportions. The American Heart Association reported that in 2004, 310,000 sudden cardiac deaths occurred in the United States and about two-thirds of unexpected cardiac deaths occurred without previous recognition of cardiac disease (Rosamond et al., 2008). This leaves a significant burden on surviving family members and those who may be at risk of a sudden cardiac event. Often, cardiac arrhythmias go unnoticed and the events that trigger them are difficult to predict. Increasing evidence suggests that the autonomic nervous system (ANS) plays a role as a trigger and predisposing factor in arrhythmia pathogenesis, making it a potential therapeutic target in the treatment of cardiac arrhythmias.

The term “autonomic nervous system” (ANS) was first coined by Langley (Langley, 1921) and has been implicated in numerous conditions including abnormalities of the heart (Fig. 1A). The heart receives input from both the sympathetic and parasympathetic systems, regulating heart rate, rhythm and contractility. Sympathetic innervation to the heart originates mainly from the right and left stellate ganglia. On the other hand, cardiac parasympathetic activity is mediated through the vagus nerve which originates in the medulla. The effects of the sympathetic system are mediated primarily through the actions of the neurotransmitter norepinephrine (noradrenaline) on alpha and beta adrenergic receptors together with co-transmitters, including neuropeptide Y and galanin (Shivkumar et al., 2016). Enhanced sympathetic stimulation increases discharge of the sinoatrial node (SAN) and augments atrioventricular node (AVN) conduction leading to an increase in heart rate and contractility. The parasympathetic systems effects are mediated primarily through acetylcholine activation of muscarinic and preganglionic nicotinic receptors and results in decreased heart rate and contractility.

The distribution of sympathetic and parasympathetic innervation within the heart varies (Fig. 1B). A gradient exists in sympathetic innervation from atria to ventricles and from base to apex of the heart. The atria are more densely innervated than the ventricles, but the

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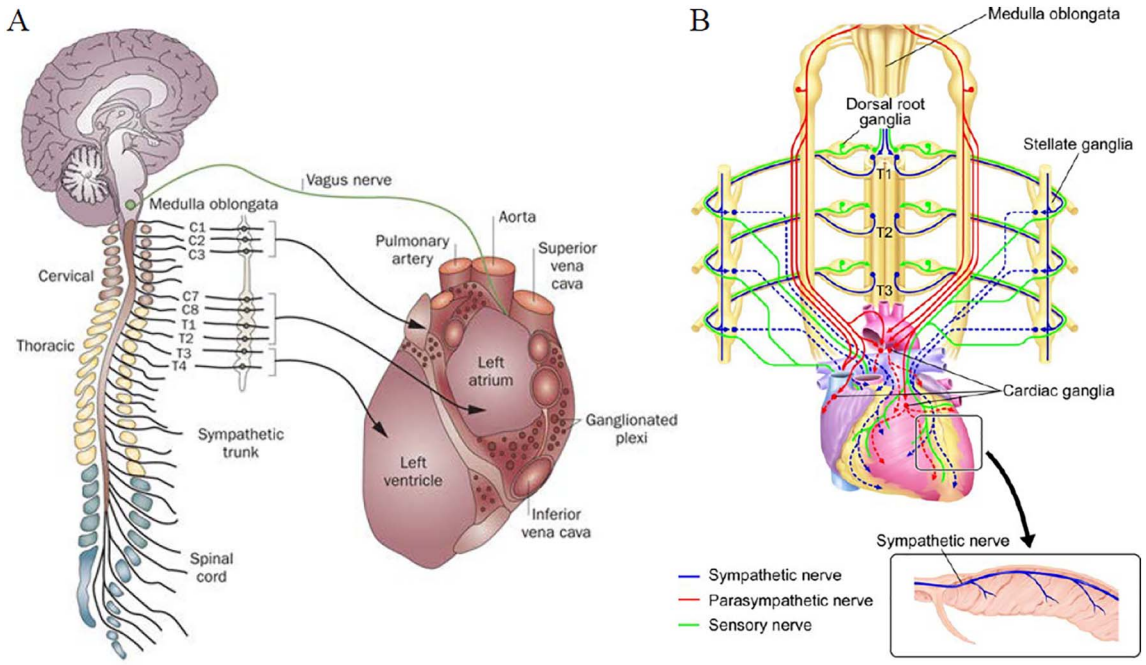

Fig. 1. Anatomy and distribution of the cardiac nervous system. A) The cardiac sympathetic ganglia consist of cervical, stellate and thoracic ganglia. The parasympathetic innervation originates from the vagus nerve. Reprinted from Shen et al., 2012 by permission from Nature Publishing Group, Copyright 2012. B) The sympathetic nerves (blue) extend from the stellate ganglia to the SAN and AVN. The parasympathetic nerves (red) extend from the vagus nerve which originates from the medulla to the base of both atria. The inset demonstrates the distribution of the sympathetic nerves in the ventricles. Reprinted from Kimura et al., 2012 by permission from Wolters Kluwer Health, Inc., Copyright 2012. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

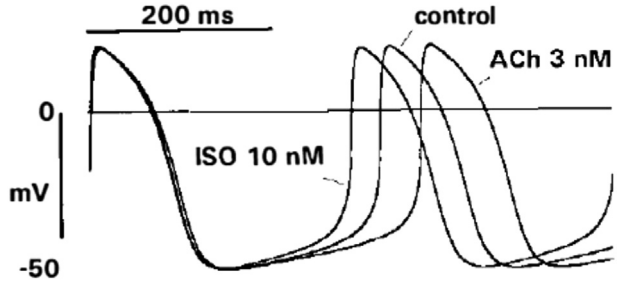

Fig. 2. Effects of isoproterenol or acetylcholine on action potential frequency of a single sinoatrial node cell. Typical action potentials of an isolated SA nodal myocyte under control conditions ("control"), in the presence of 10 nM isoproterenol ("ISO") or 3 nM acetylcholine ("ACh"). Isoproterenol, which activates the sympathetic system, increases action potential frequency whereas acetylcholine, which activates the parasympathetic system, slows action potential frequency. No effect of either neurotransmitter was seen on action potential shape or duration and was attributed to the low concentrations used. Reprinted from DiFrancesco, 1993 by permission from Annual Reviews, Copyright 1993.

ventricles are also supplied with a very thick sympathetic network at the base. Parasympathetic neurons are dispersed much more heterogeneously throughout the heart with dense innervation of the SAN and AVN, and to a lesser extent to the atria. In addition, the right ventricle is more densely innervated than the left ventricle and the left ventricular endocardium is more densely innervated than the right ventricular endocardium (Kimura et al., 2012). The intrinsic cardiac ganglia and interneurons process information from both the sympathetic and parasympathetic systems, as well as myocardial sensory neurons, and send projections to other cardiac ganglia (Armour, 1999). Imbalance between the two branches of the autonomic nervous system (sympathetic vs parasympathetic stimulation) may cause clinically relevant perturbations in cardiac physiology. Effects of the sympathetic to increase and parasympathetic nervous system to decrease the cardiac action potential frequency are demonstrated in Fig. 2. Like norepinephrine, isoproterenol activates the sympathetic nervous system through beta receptors increasing action potential frequency whereas acetylcholine, which acts primarily on the parasympathetic system, slows action potential frequency. Enhanced parasympathetic influence on the heart is generally antiarrhythmic and antifibrillatory (Vanoli et al., 1991; Lown and Verrier, 1976) while increased sympathetic influence is generally pro-arrhythmic (Schwartz et al., 1992).

2. Development of the ANS and innervation patterning play a role in arrhythmia pathogenesis

The development of the ANS is an important component in understanding autonomic pathophysiology, since an early genetic error affecting ANS development could have profound implications on autonomic cell populations (Axelrod et al., 2006). The cells of the ANS originate from the multipotential neural crest cells (Axelrod et al., 2006). These cells migrate and eventually evolve into sensory and autonomic ganglia. Several key transcription factors have been identified as critical for development of the ANS: the *MASH1* (mammalian achaete-scute homologue) and *PHOX2* (paired-like homeobox 2) genes are necessary for differentiation of uncommitted neural crest cells to the developing ANS (Sommer et al., 1995; Tiveron et al., 1996). Differentiation into functional mature neurons is incumbent on exposure to growth factors released by structures along the migratory route and within the target tissue. Nerve growth factor (NGF) in the embryonic neuron promotes migration from the neural crest and enhances maturation through neurite outgrowth. In addition to promoting cardiac neuronal survival, NGF mediates axonal growth and synapse formation during development. In the mature neuron, NGF dependence decreases but continues to enhance neurotransmitter synthesis (Thoenen and Barde, 1980). Interestingly, NGF infusion after myocardial infarction resulted in enhanced myocardial nerve sprouting (Fig. 3), and increased the incidence of ventricular tachyarrhythmias and sudden death (Cao et al., 2000). These results confirm the importance of NGF for regulating sympathetic neuron development and cardiac innervation. In addition to NGF, signaling through NT-3, which is derived from vascular smooth muscle cells, is thought to be tightly coupled to NGF in promoting sympathetic axon extension along