Modulation of Cardiac Potassium Current by Neural Tone and Ischemia

Todd T. Tomson, MD and Rishi Arora, MD
Northwestern University Feinberg School of Medicine, Bluhm Cardiovascular Institute Chicago, Illinois

SYNOPSIS

The cardiac action potential is generated by intricate flows of ions across myocyte cell membranes in a coordinated fashion to control myocardial contraction and the heart rhythm. Modulation of the flow of these ions in response to a variety of stimuli results in changes to the action potential. Abnormal or altered ion currents can result in cardiac arrhythmias. Potassium currents are particularly important for determining the cardiac action potential duration and repolarization. The autonomic nervous system plays an important role in the modulation of cardiac electrophysiology and has a particularly important role in modulation of potassium currents. Abnormalities of autonomic regulation of potassium current play a role in the genesis of cardiac arrhythmias, and alterations in acetylcholine-activated potassium channels may play a key role in atrial fibrillation. 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, particularly ventricular fibrillation.

Keywords

Autonomic nervous system; Cardiac arrhythmias; Potassium channels; Acetylcholine-activated potassium channel; ATP-sensitive potassium channel; Atrial 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.

Correspondence: Rishi Arora, MD, Northwestern University-Feinberg School of Medicine, 251 East Huron, Feinberg 8-503, Chicago, IL 60611, fax: 312-926-6295, phone: 312-503-3217, r-arora@northwestern.edu.

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While 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 autonomic nervous system 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 autonomic nervous system 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 autonomic nervous system is useful in understanding the effects of the autonomic system in normal and diseased states. The cardiac autonomic nervous system can be divided into extrinsic and intrinsic systems, with the extrinsic autonomic nervous system comprising nerves outside the heart and the intrinsic autonomic nervous system made up of nerves and ganglia within the pericardium and on the epicardial surface [1, 2]. (See Figure 1.)

The extrinsic cardiac autonomic nervous system consists of sympathetic and parasympathetic nerves. Pre-ganglionic sympathetic neurons originate in the spinal cord and travel to the pre-vertebral autonomic ganglia, including the superior cervical ganglia, the stellate ganglia, and the thoracic ganglia [3, 4]. The cell bodies of the post-ganglionic sympathetic neurons reside in these ganglia, and post-ganglionic sympathetic neurons travel from these ganglia to innervate both the atrial and ventricular surface of the heart via the superior, middle, and inferior cardiac nerves. Pre-ganglionic 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 autonomic nervous system 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, the posteromedial left atrium, and the inferolateral left atrium, and they have been noted to be close to the pulmonary vein 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 here [6–8]. In response to stimulation, post-ganglionic 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 seven transmembrane domain G-protein coupled receptors. Three subtypes of β-receptors exist, with the β-1-receptors being 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 three subunits, Ga, Gβ, and Gγ. When stimulated by norepinephrine, the β-1-receptor triggers conversion of guanosine triphosphate (GTP) to guanosine diphosphate (GDP) on the Ga subunit of the G-protein, causing Ga to dissociate from Gβ and Gγ. The primary Ga subunit associated with β-receptors is the stimulatory GaS subunit. The dissociated GaS subunit is then free to activate adenylyl cyclase, which converts adenosine triphosphate (ATP) to cyclic adenosine monophosphate (cAMP), the primary second messenger for the β-receptors. cAMP then activates protein kinase A (PKA), which phosphorylates a variety of proteins involved in calcium handling, including the L-type calcium channel, the ryanodine receptor, and phospholamban, resulting in enhanced calcium cycling. In addition, sympathetic stimulation also affects several potassium channels, particularly activation of the slow and rapid delayed rectifier potassium channel (IKs and IKr, respectively), which offsets the inward current that results from enhanced calcium inflow [9–12]. (See Figure 2.)

The parasympathetic neurons exert their influence on cardiac myocytes through the release of acetylcholine (ACh). ACh binds to the M2 muscarinic receptor on the myocyte surface. The M2 receptor is another G-protein coupled receptor [6]. The Ga subunit associated with the muscarinic receptor is the inhibitor Gai subunit. When ACh binds to the M2 receptor, the receptor catalyzes the conversion of GTP to GDP on the Gai subunit of the G-protein coupled to the receptor. Conversion of GTP to GDP causes release of the Gai subunit from the Gβγ subunit, freeing the Gβγ subunit. In the case of parasympathetic stimulation, the Gβγ subunits are the active subunits and are responsible primarily for activation of the ligand-gated potassium channel IK-ACh. IK-ACh is the predominant ion channel responsible for parasympathetic effects on the action potential duration and effective refractory period of the atrium [13]. IK-ACh activation leads to action potential duration shortening that may be necessary for promoting abnormal atrial rhythms, such as atrial fibrillation and atrial tachycardias.

Autonomic Effects on Atrial Potassium Currents

Sinoatrial Node and Heart Rate

The autonomic nervous system is the primary system responsible for modulating cardiac pacemaker cell automaticity and thus heart rate [14]. With brief reference to potassium currents, activation of IK-ACh channels in the sinoatrial (SA) nodal and atrioventricular (AV) nodal tissue in response to parasympathetic stimulation is a major mechanism by which parasympathetic stimulation reduces heart rate and slows conduction in the AV node. Activation of IK-ACh in the pacemaker cells of the SA node leads to cell membrane
hyperpolarization, which decreases spontaneous firing of the SA node and reduces heart rate [15]. In addition to the effects on I_{K-ACh}, parasympathetic stimulation more directly opposes sympathetic stimulation by causing a decrease in the funny current (I_f) and the L-type calcium current (I_{CaL}) [16, 17]. The combination of these effects results in hyperpolarization and a slower automatic depolarization of the SA nodal cells, resulting in a reduced heart rate. While parasympathetic stimulation exerts its influence on heart rate in a large part through activation of I_{K-ACh} channels, the effect of sympathetic stimulation is driven primarily by effects on I_f and I_{CaL}, with sympathetic stimulation resulting in an increased heart rate by enhancing the activity of both I_f and I_{CaL} [14, 18]. However, sympathetic stimulation also effects the activity of I_{Ks} and I_{Kr} currents, which also play a part in regulating automaticity and in leading to the action potential shortening necessary at more rapid heart rates.

**Atrial Myocardium and Atrial Arrhythmias**

Autonomic effects on myocardial potassium currents are most prominent in the atria, and imbalances in the autonomic nervous system and the subsequent effects on potassium currents may play a role in the genesis of diseases, such as atrial fibrillation (AF), the most common sustained arrhythmia in clinical practice. Several studies have demonstrated an association between autonomic effects and AF. For example, exercise-induced AF may be sympathetically driven [19], while the parasympathetic nervous system may play a role in AF in young patients with no structural heart disease [20]. The unique autonomic innervations of the left atrium (LA) and the autonomic effects on potassium currents, particularly I_{K-ACh}, may be a key contributor to AF. While there are autonomic nerves throughout the atria, this innervation is heterogeneous. The pulmonary veins and posterior left atrium have a unique autonomic profile in comparison to the rest of the atria, and these differences in autonomic innervations and the subsequent electrophysiologic effects on potassium currents may play an important contributing role in the genesis of arrhythmias like AF.

The unique distribution of autonomic innervation of the PVs and PLA was demonstrated in a canine study by Arora et al [21]. In this study, the distribution and physiology of sympathetic and parasympathetic nerves in various parts of the LA was investigated. The study found that both parasympathetic and sympathetic fibers most richly innervated the posterior LA (PLA), with nerve bundles colocalized mainly in fibrofatty tissue but also in the surrounding myocardium. (See Figure 3.) In the PLA, parasympathetic nerves were more numerous than sympathetic nerves. Not only did autonomic nerves localize to the PLA, with a predominance of parasympathetic fibers but M2 receptor density was also significantly more pronounced in the PLA than in the rest of the LA. Finally, the study showed that since the majority of parasympathetic fibers and M2 receptors in the LA are located in the PLA, selective parasympathetic blockade in the PLA significantly altered vagal responsiveness in the entire LA. These findings were applied to the effects on AF inducibility. Selective blockade of the parasympathetic effects in the PLA resulted in attenuation of parasympathetic effects in the entire LA and resulted in near complete elimination of vagal-induced AF in this model, demonstrating the importance of the PLA and parasympathetic activity in the induction of AF.

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Another canine study by Arora et al specifically investigated the electrophysiologic profile of the PVs and LA and found heterogeneous electrophysiologic responses in the LA [22]. (See Figure 4.) In this study, the effect of modulating autonomic tone on effective refractory periods (ERPs) in various part of the LA was investigated. In addition, these findings were correlated with $I_{K-ACh}$ distribution within the LA. The study showed autonomic stimulation resulted in a greater degree of ERP change in the LAA compared to the PV and PLA. These findings correlated with a greater concentration of $I_{K-ACh}$ channels expressed in the LAA compared to the rest of the LA. Interestingly, while the cumulative effect of changes in autonomic tone was greatest in the LAA, the heterogeneity of changes in ERP (measured by the variance of changes in ERP within the different areas of the LA) was significantly greater in the PLA than the LAA. This increased heterogeneity in ERP changes in response to autonomic tone within the PLA correlated with a more heterogeneous distribution of $I_{K-ACh}$ channel concentration within the PLA, as identified by immunohistochemical staining. Other studies have shown that $I_{K-ACh}$ concentrations are higher in the LA than the RA [23], but this study highlights the heterogeneity of $I_{K-ACh}$ distribution within the tissue of the LA. Since heterogeneity of ERP shortening within the LA is thought to be a major contributor to the induction and maintenance of AF, allowing for reentry within the atrium to occur [24], the unique electrophysiologic properties of the PLA, with heterogeneous $I_{K-ACh}$ distribution and ERP changes in response to changes in autonomic tone, in combination with the previous study’s finding of increased parasympathetic nerve innervations and M2-receptor concentration in the PLA suggest the importance of the PLA as a contributor to AF induction. These data also support the idea that $I_{K-ACh}$ plays an important role in vagal influence on AF [25].

Human studies have also confirmed the heterogeneous distribution of autonomic nerves in the atria. In a human study by Chevalier et al, heterogeneous nerve distribution was described in the region of the PV and surrounding left atrium [26]. The study showed higher concentrations of epicardial nerve fibers and ganglia at the ostia of the four pulmonary veins and in the posterior left atrium. Tan et al also demonstrated that the highest concentrations of autonomic nerves were at the junction of the PVs and the LA and that sympathetic and parasympathetic nerves were co-localized in the human left atrium[27]. A human study by Deneke et al again showed that nerve density was higher in the region of the PV ostia and antrum compared to other areas of the atria [28]. The study also demonstrated a high degree of colocalization of sympathetic and parasympathetic nerves within the atria. These findings in humans seem consistent with the findings of animal studies.

While the above studies investigated the heterogeneous autonomic innervations of the LA and the heterogeneous effects of modulation of autonomic tone in the LA potassium channels and currents in normal subjects, studies have also investigated changes in autonomic innervations of the atria, and subsequent effects on potassium current, seen in the setting of structural heart disease and shown that these autonomic alterations may play a role in the genesis of AF. Ng et al studied the effects of congestive heart failure (CHF) on autonomic remodeling in the atria and subsequent changes in the electrophysiologic properties of the atria in a canine model of CHF [29]. In this study, CHF was induced by rapid ventricular pacing over a period of weeks. CHF dogs demonstrated remodeling of both the sympathetic and parasympathetic innervations of the LA. In both normal and CHF dogs,
Autonomic nerves were located in the fibrofatty tissue overlaying the epicardium, with colocalization of both sympathetic and parasympathetic nerves. In CHF, autonomic innervation was increased in the LA, as noted by increases in nerve bundle size and density of cardiac ganglia. Neural remodeling was most prominent in the PVs and PLA, which correlates with the baseline increased innervations of the PLA discussed earlier. Sympathetic remodeling was suggested by both an increase in sympathetic nerve fiber density and an increase in $\beta$-1-receptor density, which was accompanied by an increased effect of sympathetic stimulation on atrial ERPs, particularly in the PLA and PVs. The increased parasympathetic innervation, on the other hand, was not associated with any change in the M2-receptor activity, which remained unchanged compared to control dogs. This observation was accounted for by an increase in acetylcholinesterase activity, which caused a reduction in synaptic acetylcholine and thus a reduction in M2-receptor stimulation. These changes led to a decreased effect of parasympathetic stimulation on atrial ERP, likely through altered effects on $I_{K-ACh}$ potassium current. Despite the decreased parasympathetic responsiveness of the LA, some effect of parasympathetic tone was maintained in the LA. The continued effect of parasympathetic tone was demonstrated most importantly by the fact that parasympathetic blockade led to a significant decrease in the duration of induced AF, which also suggests that parasympathetic activity is an important contributor to AF substrate in CHF and that parasympathetic blockade may be a potential target for AF treatment. Both sympathetic and parasympathetic blockade together did not result in a further decreased in AF duration, although it did decrease AF dominant frequency. This finding suggests that the sympathetic innervation may play a more modulatory role in AF induction and that parasympathetic innervation and its downstream effects on potassium current is the dominant autonomic limb affecting the atrium in CHF.

Canine models of AF induced by rapid atrial pacing (RAP) have also been used to study the effects of AF on autonomic innervation and atrial electrophysiology. A study by Jayachandran et al. showed that RAP-induced AF in dogs resulted in both autonomic and electrophysiological remodeling of the atria [30]. Following four weeks of rapid atrial pacing, all paced dogs developed sustained AF. Positron emission tomography of the atria was performed using [C-11] hydroxyephedrine (HED) to label sympathetic nerve terminals. HED activity in the atria was significantly greater in the atria of paced dogs, and these findings correlated with increased norepinephrine levels in atrial tissue samples of paced dog, suggesting an increased sympathetic innervation in paced dogs with AF. HED retention was also noted to be significantly more heterogeneous in the atria of paced dogs compared to controls, which correlates with the findings in CHF models of AF. Another study by Chang et al. looked at histologic evidence for autonomic changes in a canine models of RAP-induced AF [31]. Dogs that had sustained AF induced by RAP had a significantly higher density of atrial sympathetic innervation compared to control animals. In addition, the histologic data showed a heterogeneous distribution of nerves within the atria, correlating with the imaging data from the previous study. These finding suggest the importance of autonomic changes in AF and likely underlie some of the changes in potassium current seen in AF. In another study, Nishida et al. investigated the effects of pulmonary vein encircling ablation and linear left atrial roof lines on AF induced by rapid atrial pacing in a canine model [32]. Pulmonary vein encircling ablation, which can affect autonomic ganglia near the
pulmonary veins and result in autonomic denervation, suppressed AF initiation in this canine model by prolonging left atrial ERPs.

Similar changes in autonomic innervation in subjects with AF have also been observed in human subjects. Gould et al. investigated atrial sympathetic innervation in patients with and without AF undergoing cardiac surgery [33]. The right atrial appendage of twenty four patient (half in sinus rhythm and half in persistent AF) were collected during surgery, and the degree of sympathetic innervation was examined by immunostaining for sympathetic nerves. Sympathetic innervation was significantly higher in the atrial tissue of the AF cohort compared to the patients in sinus rhythm. In addition, right atrial tissue was more densely innervated than left atrial tissue in patients with AF. The heterogeneously increased sympathetic innervation seen in patients with persistent AF corresponds to that seen in the animal models. Interestingly, sympathetic innervation seems to increase the most in the right atrium, whereas changes in parasympathetic innervation seem to be greatest in the left atrium. This heterogeneity of autonomic innervation and its subsequent effects on potassium currents and atrial ERPs may play a role in the initiation and maintenance of clinical AF.

These studies demonstrating the heterogeneous effects of autonomic innervation in both normal hearts and in the setting of structural heart disease highlight the importance of the autonomic nervous system as a contributing factor to atrial arrhythmias. These data also underscore the potential importance of the autonomic nervous system as a suitable therapeutic target in AF in both normal and diseased hearts.

A final potassium current in the atria that is at least indirectly modulated by the autonomic system is the small conductance calcium-activated potassium (SK) current. SK channels also likely may play a role in the cardiac arrhythmias. They are sensitive to intracellular calcium levels and link intracellular calcium concentrations and cellular membrane potentials at the myocyte level and are important in modulation of action potential duration and repolarization, particularly of atrial myocytes [34-35]. SK channels have been found to be upregulated in heart failure in both animal models and in humans [36-39]. Although a specific modulation of the SK channel by the autonomic nervous system has not been clearly shown, some studies suggest that SK channels play a role in AF [40-41], possibly by modulating the membrane potentials in response to different calcium loading situations that result from different degrees of sympathetic stimulation. As such, SK current may represent a therapeutic target for AF treatment.

**Modulation of Autonomic Effects on Atrial Potassium Current as a Possible Therapeutic Target for AF**

The observations that the autonomic nervous system modulates atrial myocardial electrophysiologic properties, particularly through parasympathetic alterations in \( I_{K-ACh} \), have led to the idea that modulation of the intrinsic cardiac nervous system maybe one therapeutic avenue for the treatment of atrial arrhythmias, particularly AF. At a gross anatomic level, ganglionated plexi ablation has been attempted as a way of reducing autonomic innervation of the LA and thus reducing AF burden by limiting the effects of the autonomic nervous system on the atria. One method of ablating ganglionated plexi is to use
high-frequency stimulation to identify ganglionated plexi at the time of ablation, and use of this method to identify ganglionated plexi for ablation in addition to standard pulmonary vein isolation has shown promising results in treating AF [42]. Another approach to autonomic denervation is an anatomically based approach to ablation. A randomized controlled trial performed by Katritsis et al showed the benefit of anatomically based GP ablation for AF [43]. In this trial, 242 patients with paroxysmal AF were randomized to either standard PV isolation, anatomic ablation of left atrial GP, or standard PV isolation plus left atrial GP ablation. At 2 years of follow-up, patients who received standard PV isolation plus left atrial GP ablation had a significantly higher freedom from recurrent AF (74%) compared to either PV isolation alone (56%) or left atrial GP ablation alone (48%). A recent meta-analysis of cardiac autonomic denervation in addition to standard PV ablation for AF also suggests improved freedom from recurrent AF with cardiac autonomic denervation [44]. This strategy of treating AF may be effective because cardiac autonomic denervation reduces the heterogeneity of ERP changes in the left atrium seen as a result of the autonomic nervous systems effect on heterogeneously distributed potassium channels, particularly in the PLA where much of the ablation is performed.

In addition to modification of the gross anatomy of the LA by ablation, more targeted approaches of modulating the potassium currents in the atria through alteration in cell signaling at a cellular level may also be a target for AF treatment. A targeted approach to modulating the autonomic nervous system’s effects on potassium current is of interest because there are several drawbacks to the current strategy of GP ablation. First, since sympathetic and parasympathetic fibers are co-localized, ablation will non-selectively destroy both limbs of the ANS. Second, ablation carries other risks, such as damage to the atrial myocardium or other structures surrounding the LA. Third, since ablation targets only specific areas, some nerves could be left unaffected by ablation, limiting the overall effect of ablation. Given these drawbacks, a more targeted approach to modulation of the ANS using molecular or biologic approaches to target ANS cell signaling have been investigated.

One biologic approach to treating AF is to modulate $I_{K-ACh}$ activity and potassium current by targeting the parasympathetic G-protein coupled receptor signaling mechanism. As mentioned previously, M2-receptor stimulation by the parasympathetic nervous system leads to activation of the $I_{K-ACh}$ through a G-protein coupled mechanism, leading to increased potassium current and atrial effective refractory period shortening that promotes initiation and maintenance of AF. Aistrup et al have shown in two studies that inhibition of G-protein signaling in the atrium can lead to attenuated parasympathetic effects in the atrium [45].

In a proof of concept animal study, G-protein inhibitory peptides targeting the C-terminus of the $G_{alpha}i/o$ subunit, the subunit associated with parasympathetic M2-receptors, were used to inhibit parasympathetic signaling in the atrium [46]. Peptides targeting the C-terminal portion of $G_{alpha}i$ were selectively delivered to the PLA by direct injection into the myocardium with associated electroporation. These $G_{alpha}i$ C-terminal peptides ($G_{alpha}ictp$) selectively inhibited parasympathetic signaling by disrupting binding of the native $G_{alpha}i$ to the G-protein complex associated with the M2-receptor and reducing signal transduction. Injection of these inhibitory peptides into the PLA resulted in prolongation of the atrial ERP both at baseline and during parasympathetic stimulation, demonstrating the effects of reduced activation of $I_{K-ACh}$. A second animal study tested the ability of minigene plasmids
expressing inhibitory Gα C-terminal peptides to modulate parasympathetic stimulation and downstream potassium current [45]. In this gene-based approach, plasmid DNA expressing either inhibitory Gαi ctp alone or in combination with inhibitory Gαo ctp were injected into the PLA of canines and incorporated into the cells via electroporation. Effects on atrial ERPs and AF inducibility were investigated under conditions of parasympathetic stimulation. When both inhibitory Gαi ctp and Gαo ctp were expressed in the PLA, parasympathetic-induced atrial ERP shortening as well as AF inducibility were almost entirely eliminated. (See Figure 5.) Both of these studies showed that that parasympathetic denervation, resulting in decreased I_{K-ACh} activity, can be achieved on a selective basis by introduction of small inhibitory peptides in a targeted fashion into the LA.

Autonomic Control of Potassium Current in the Ventricle

While atrial fibrillation seems to be promoted by parasympathetic stimulation, parasympathetic stimulation may be protective against ventricular arrhythmias, such as ventricular fibrillation [47]. The difference in parasympathetic effect between the atrium and ventricle may be explained by differences in I_{K-ACh} distribution between the atria and ventricles, and thus the effect of parasympathetic stimulation on potassium current and refractory periods in each chamber. Whereas, I_{K-ACh} is abundant in most atrial tissue [46], I_{K-ACh} is expressed to a much lower degree in the ventricle, with ventricular myocytes having little or no I_{K-ACh} [48]. This finding may be responsible for the observed fact that, while parasympathetic stimulation significantly shortens the action potential duration in the atria, it either lengthens the action potential duration [49] or shortens it by a significantly smaller amount in the ventricle [50-51].

While there is little I_{K-ACh} in ventricular myocardium, the ANS may exert effects on ventricular potassium currents through effects on the slowly and rapidly activated delayed rectifier currents (I_{Ks} and I_{Kr}, respectively), which are largely responsible for the repolarization phase of the cardiac action potential. In normal hearts, effects on these currents in response to autonomic inputs allows for dynamic control of the cardiac action potential to match diastolic filling with changes in heart rate caused by changes in autonomic tone.

I_{Ks} may be the potassium current in the ventricle that is most affected by the changes in sympathetic stimulation [52]. Sympathetic stimulation through the β-receptor results in an increased I_{Ks} current, through protein kinase A-mediated phosphorylation of the KCNQ1 subunit, and shortens the action potential duration and thus myocardial repolarization, which is necessary to ensure diastolic filling time during higher heart rates that also result from sympathetic stimulation. Loss-of-function mutations in the KCNQ1 subunit of the I_{Ks} channel are linked to the most common long-QT syndrome, long-QT syndrome type 1 (LQTS 1), which is associated with prolongation of the cardiac action potential and sudden death [53]. Adverse events and cardiac arrhythmias in patients with LQTS 1 are particularly associated with activities, such as exercise or swimming, in which sympathetic stimulation would normally result in increased I_{Ks} current [54]. However, in patients with LQTS 1 and mutations in the I_{Ks} channel subunit, sympathetic stimulation paradoxically tends to cause APD prolongation, presumably because of an imbalance in the repolarizing I_{Ks} current and
other ion currents. Modulation of the autonomic nervous system with beta blocking drugs that reduce sympathetic stimulation on the heart has been shown to reduce the risk of adverse events in patients with LQTS 1 [55].

The other main delayed rectifier potassium current, I_{Kr}, may also be regulated by the autonomic nervous system in the ventricle. Like I_{Ks}, I_{Kr} is involved in the repolarization phase of the cardiac action potential. Mutations in the KCNH2 subunit of I_{Kr} are associated with the second most common form of long-QT syndrome, LQTS 2 [56]. Sympathetic stimulation modulates I_{Kr} current in a variety of ways. Sympathetic stimulation, through the activation of G_{alpha}, results in an increase in intracellular cAMP concentration, which can directly interact with the I_{Kr} channel, and in PKA-dependent phosphorylation of the I_{Kr} channel [9–10].

Modulation of Ventricular Autonomic Tone as a Treatment of Ventricular Arrhythmias

As in the atrium, where ablation of autonomic ganglia may serve as a method of reducing atrial arrhythmias, modulation of autonomic input to the ventricle may reduce the risk of ventricular arrhythmias. Autonomic denervation of the ventricle by cervical sympathectomy alters sympathetic stimulation of the ventricle and can reduce the risk of ventricular arrhythmias in some patients, particularly in patients with syndromes associated with congenital sudden cardiac death such as LQTS and catecholaminergic polymorphic ventricular tachycardia [57–59]. Another method of modulating autonomic input to the ventricle which may be effective in reducing ventricular arrhythmias is spinal cord stimulation, which may result in parasympathetic stimulation and sympathetic inhibition [60–61]. These therapeutic treatments for ventricular arrhythmias almost certainly exert their antiarrhythmic effect, at least in part, by reducing the modulation of autonomic stimulation-associated changes in potassium current in the myocardium. Further elucidation of the exact mechanism by which modulation of the extrinsic autonomic system leads to antiarrhythmic effects, particularly on potassium current modulation, may lead to the identification of more specific targets for treatments of ventricular arrhythmias.

Effects of Ischemia on Potassium Currents

In addition to autonomic stimulation, other factors such as ischemia can modulate the cardiac potassium current. The ATP-sensitive inwardly rectifying potassium channel (I_{K,ATP}), which is inhibited by ATP, modulates potassium current as a function of the metabolic state of the heart [62]. Under normal conditions with a normal intracellular ATP/ADP ratio, I_{K,ATP} remains closed. During states of ischemia or hypoxia, the relative concentration of ATP to ADP decreases. The decreased ATP/ADP ratio that results from ischemia leads to activation of I_{K,ATP}, helping to preserve the resting membrane potential and to reduce the cardiac action potential duration, cardiac contraction, and thus energy/ATP usage during times of stress on the myocardium. In this way, I_{K,ATP} may function to protect the myocardium from the effects of ischemia. Indeed, knockout mice lacking Kir6.2, a the pore-forming subunit of I_{K,ATP}, have a reduced ability to perform exercise, a compromised cardiac performance in response to sympathetic stimulation, and an increased susceptibility
to arrhythmias and sudden death as a response to sympathetic stimulation [63]. I\textsubscript{K-ATP} may also play a role in ischemic preconditioning, the phenomenon whereby brief periods of ischemia followed by reperfusion can result in reduced myocardial injury to an ischemic insult. Animal studies have shown not only that agonists of the I\textsubscript{K-ATP} channel reproduce the effects of preconditioning but also that I\textsubscript{K-ATP} blockers prevent the protective effects of ischemic preconditioning [64-66]. While the initial activation of I\textsubscript{K-ATP} in response to ischemia may be protective, prolonged I\textsubscript{K-ATP} activation may actually lead to early repolarization and thus may be pro-arrhythmic [67]. In fact, early repolarization syndromes associated with ventricular fibrillation have been associated with gain of function mutations in the I\textsubscript{K-ATP} channel [68, 69].

Modulators of I\textsubscript{K-ATP} channel activity may be a potential target for anti-arrhythmic and anti-ischemic mediations. I\textsubscript{K-ATP} activators and inhibitors generally act on the SUR (for sulfonylureas) subunit of the channel. I\textsubscript{K-ATP} channels are present in many tissues, including cardiac myocytes, insulin-secreting pancreatic cells where they regulate insulin secretion, and vascular smooth muscle where they regulate muscle constriction. Non-selective I\textsubscript{K-ATP} blockers or activators may, therefore, cause abnormalities in regulation of blood glucose levels or blood pressure through their effects on other tissue. However, cardiac specific I\textsubscript{K-ATP} blockers have the potential to reduce the effects of ischemia on cardiac action potential shortening without the sided effects of non-selective agents [70-71]. On the other hand, I\textsubscript{K-ATP} channel openers may be useful in simulating ischemic preconditioning and may be protective in the setting of acute ischemia [71]. Again, selective activators of I\textsubscript{K-ATP} are needed to avoid the unwanted side effects, such as unwanted changes in blood pressure, from changes in activation of I\textsubscript{K-ATP} in vascular smooth muscle. Focus has been placed on evaluating the properties of drugs that have specificity for either the sarcolemmal or the mitochondrial I\textsubscript{K-ATP} channels. Mitochondrial I\textsubscript{K-ATP} activators, in particular, have shown promising anti-ischemic properties with minimal side effects on vascular tone [72].

**Conclusions**

Modulation of the potassium current in the heart plays an important part in cardiac electrophysiology by altering the cardiac action potential duration. The autonomic nervous system is one major modulator of the cardiac potassium current. Changes in autonomic tone in response to changes in physiologic states lead to physiologic alterations in potassium current, affecting cardiac action potential duration and repolarization. Abnormalities of autonomic regulation, such as those seen in heart failure, may contribute to cardiac arrhythmias. Understanding the mechanisms by which the autonomic nervous system alters potassium current to cause diseases, such as atrial fibrillation, can potentially lead to more targeted treatments of these conditions. The same holds true for understanding other modulators of potassium currents, such as the effect of ischemia on ATP-sensitive potassium currents, a better understanding of which could lead to improved management of cardiac arrhythmias.
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### Key Points

1. 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 in cardiac arrhythmias.

2. The autonomic nervous system have a role in regulation of cardiac potassium currents, and abnormalities in autonomic regulation of cardiac potassium currents can result in arrhythmias, including atrial fibrillation that may result from abnormal modulation of acetylcholine-activated potassium channels.

3. 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, particularly ventricular fibrillation.
Figure 1.
Autonomic innervations of the heart. The extrinsic autonomic nervous system 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 autonomic nervous system 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, Lin SF, Fishbein MC, Chen LS, Chen PS. Neural mechanisms of atrial arrhythmias. Nat Rev Cardiol. 2011;9:30–39; with permission.
Figure 2.
Sympathetic and parasympathetic signaling pathways. ACh indicates acetylcholine; PLB, phospholamban; PKA, protein kinase A; β-AR, β-adrenergic receptor; Epi, epinephrine; Norepi, norepinephrine; RyR, ryanodine receptor; M2 Rec, M2 receptor. Adapted from Arora R. Recent Insights into the Role of the Autonomic Nervous System in the Creation of Substrate for Atrial Fibrillation – Implications for Therapies Targeting the Atrial Autonomic Nervous System. Circ Arrhythm Electrophysiol. 2012;5:850–859; with permission.
Figure 3.
Figure 4.
Differences in heterogeneity of parasympathetic-induced effective refractory period (ERP) shortening correspond with differences in heterogeneity of $I_{K-ACh}$ distribution in the posterior left atrium (PLA) and left atrial appendage (LAA). A. Heterogeneity in ERP shortening (measured as $\sqrt{\text{Variance}}/N$) is greater in the PLA than the LAA. B. Staining for $I_{K-ACh}$ in the LAA is very homogeneous. C. Staining for $I_{K-ACh}$ in the PLA is significantly more heterogeneous, with arrows indicating areas of heterogeneous staining. PV indicates pulmonary vein. Adapted from Arora R, Ng J, Ulphani J, et al. Unique autonomic profile of the pulmonary veins and posterior left atrium. J Am Coll Cardiol. 2007;49:1340–1348; with permission.
Figure 5.
Reduction in parasympathetic stimulation-induced effective refractory period (ERP) shortening in the canine posterior left atrium (PLA) by plasmid DNA vectors (mini-genes) expressing $\alpha_i$ C-terminal peptide ($\alpha_{i\text{ctp}}$) injected in the PLA either alone or in combination with a minigene expressing $\alpha_o\text{ctp}$ compared to injection of a control minigene expressing scrambled peptide ($\alpha_{R\text{p}}$). Adapted from Aistrup, G.L., et al., Targeted nonviral gene-based inhibition of $\alpha(i/o)$-mediated vagal signaling in the posterior left atrium decreases vagal-induced atrial fibrillation. Heart Rhythm, 2011. 8(11): p. 1722–9; with permission.