Molecular Mechanisms of Sympathetic Remodeling and Arrhythmias

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A variety of pathological conditions can increase risk for development of ventricular arrhythmias in humans including diabetes mellitus, obesity, myocardial infarction (MI), and heart failure. Many of these diseases involve global disruption of the autonomic nervous system, including increased sympathetic drive and parasympathetic withdrawal, but another common factor among these disorders is sympathetic dysfunction within the heart. Treatments that target cardiac sympathetic transmission, including β-blockers and ganglionectomy, prolong life and decrease arrhythmias.[1–5]

Sympathetic control of the heart under normal conditions occurs primarily via norepinephrine acting on β adrenergic receptors (β-AR) to stimulate increases in heart rate (chronotropy), conduction velocity (dromotropy), and contractility (inotropy). These positive effects of sympathetic stimulation allow myocytes to meet increased cardiac demands during stress or exercise, serving to maintain homeostasis. The nervous system adapts to changing conditions, however, and sympathetic neurons undergo structural and functional alterations in response to injury and disease. There are at least 4 types of sympathetic remodeling that occur during conditions of increased arrhythmia susceptibility: hyperinnervation (increased nerve density), denervation (decreased nerve density), altered neurotransmitter or neuropeptide production and increased neuronal excitability. Rubart and Zipes[6] proposed a model to explain how these diverse changes in sympathetic transmission might contribute to arrhythmia generation, suggesting that inappropriate heterogeneity of norepinephrine release within the heart leads to differential electric remodeling of cardiac myocytes and predisposes the heart to electric instability. Many studies now support the hypothesis that heterogeneity of noradrenergic transmission increases the risk of arrhythmia and have identified some of the mechanisms that underlie neuronal remodeling. This review will examine the mechanisms of sympathetic remodeling and will connect neural changes to increased arrhythmia susceptibility. We will focus on ventricular arrhythmias because atrial arrhythmias were reviewed recently.[7]

Hyperinnervation and Excess Norepinephrine Release

Regional hyperinnervation was the first type of neural remodeling linked to arrhythmia generation in humans.[8,9] Areas of sympathetic hyperinnervation, defined as increased nerve fiber density when compared with control tissue, have now been identified in many conditions with increased arrhythmia susceptibility including heart failure,[9] MI,[10,11] spinal cord injury,[12] and diet-induced obesity.[13,14] Nerve growth factor (NGF) has been the focus of studies related to cardiac hyperinnervation because NGF stimulates the extension, or sprouting, of sympathetic nerve endings during development and after injury. Cardiac NGF is elevated in animal and human hearts during conditions associated with hyperinnervation[10,12,15] and is decreased in conditions that include a loss of functional sympathetic innervation such as late stage heart failure[16] and diabetic neuropathy.[17]

Sympathetic axon outgrowth is triggered through activation of the tropomyosin related kinase A (TrkA) receptor, which stimulates serine phosphorylation of signal transducer and activator of transcription 3 (STAT3) in addition to activating other signaling pathways. Although TrkA can be activated by both NGF and neurotrophin 3 during development, NGF is the only ligand that activates TrkA in mature sympathetic neurons, and thus is crucial for maintaining sympathetic neuron health and stimulating axon regeneration. Recent studies indicate that cytokines like leukemia inhibitory factor and cardiotrophin-1, which activate the gp130 receptor, do not stimulate axon growth on their own but are required for maximal NGF-induced sympathetic axon extension.[18] These cytokines stimulate tyrosine phosphorylation of signal transducer and activator of transcription 3, and phosphorylation of signal transducer and activator of transcription 3 on both serine and tyrosine is required for maximal axon outgrowth.[18] The related cytokine leptin also enhances sympathetic axon outgrowth[19] and may contribute to the cardiac hyperinnervation observed in diet-induced obesity.

Pathological conditions resulting in hyperinnervation within the heart are also associated with increased sympathetic drive from the central nervous system, and enhanced

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excitability of postganglionic neurons may also contribute to elevated adrenergic transmission in the heart. Neuronal cell size is increased significantly in stellate ganglia removed from humans with ischemic and non–ischemic cardiomyopathy when compared with that in control ganglia,[20] and similar changes identified in canines coincide with increased neuronal excitability.[21] Similarly, increased dendrite field size and synapse number contribute to elevated cardiac sympathetic tone in rats after T5 spinal cord transection.[22] Retrograde TrkA signaling by NGF regulates synapse formation during development[23] and high NGF likely contributes to increased cell size and synapse formation after injury. NGF may also increase sympathetic excitability by altering sensitivity to inflammatory mediators[24] and by altering neuronal firing properties.[25] Interestingly, statins decrease sympathetic neuron excitability by stimulating dendrite retraction,[26] raising the possibility that dampening sympathetic drive via peripheral actions contributes to their therapeutic value in patients with cardiovascular disease.

Functional noradrenergic transmission requires a balance between norepinephrine synthesis, release, and reuptake, each of which can be regulated independently.[27] For example, after MI newly sprouting sympathetic fibers have low norepinephrine content,[28] but there is a paradoxical increase in extracellular norepinephrine.[27] This can be explained, in part, by elevated norepinephrine synthesis and release in other regions of the heart that are not matched by a similar increase in norepinephrine removal.[11] Such functional changes have been identified in patients with heart failure, where increased norepinephrine release and decreased norepinephrine reuptake contribute to a buildup of extracellular norepinephrine and excessive activation of β-AR.[29]

Myocardial Responses to Acute Hyperinnervation/Excess Norepinephrine

Norepinephrine released from sympathetic nerves activates cardiac β-AR to modulate myocyte repolarization and contractility. Sympathetic nerves are not distributed evenly across the heart, but are most dense near the base of the ventricles. Likewise, the epicardial to endocardial gradient in cardiac action potential duration (APD)[30–32] that is critical for normal activation and repolarization of the left ventricle is regulated by innervation, and disrupting the normal organization of sympathetic nerves in an otherwise healthy heart is arrhythmogenic.[33,34] Activation of cardiac β-AR modulates myocyte repolarization by altering transmembrane currents and Ca^{2+} homeostasis.[35–37] β-AR–stimulated cAMP leads to phosphorylation of proteins involved in excitation–contraction coupling including phospholamban, L-type Ca^{2+} channels, and ryanodine receptors, resulting in increased sarcoplasmic reticulum (SR) Ca^{2+}-ATPase activity and an increase in SR Ca^{2+} content.[38] Thus, during sympathetic stimulation`, more Ca^{2+} is released from the SR[39] to activate the myofilaments, increasing contractility, but spontaneous Ca^{2+} release from the SR also becomes more likely.[40,41] Therefore, the positive inotropic effects of sympathetic stimulation that allow myocytes to meet increased cardiac demands are accompanied by an increased risk for pathological arrhythmias via focal (triggered) mechanisms.

At the cellular level, focal activity during sympathetic activation is likely because of delayed afterdepolarizations,[42] which are membrane depolarizations occurring during phase 4 of the action potential. The increased cytosolic and SR Ca^{2+} levels that occur during sympathetic activation can lead to SR Ca^{2+} overload (Figure 1), which may result in spontaneous opening of ryanodine receptors and Ca^{2+} release that is not in response to an action potential. This leads to Ca^{2+} extrusion from the cytosol via the Na^+/Ca^{2+} exchanger (NCX).[43] NCX is electrogenic, extruding 1 Ca^{2+} ion (2+) in exchange for 3 Na^+ ions (3+), which produces a net inward current. If the inward current is large enough, the cell membrane depolarizes and a triggered action potential may occur.

At the tissue level, several thousand cells must all experience delayed afterdepolarization simultaneously to generate enough depolarizing current to produce a propagating action potential (called the source–sink mismatch).[44,45] Recent studies revealed that local application of β-AR agonists such as norepinephrine or isoproterenol can induce premature ventricular complexes and sustained focal ventricular tachycardia in intact hearts,[46–49] providing a mechanistic link between the numerous experimental and the clinical investigations that have found regional hyperinnervation accompanied by increased arrhythmia risk.[8] Furthermore, electrophysiological remodeling of cardiac myocytes in response to MI or heart failure can cause changes (eg, increased expression of NCX,[50] increased SR Ca^{2+} leak through ryanodine receptor,[51] decreased inward rectifying K^+ current,[43] decreased gap junction coupling,[52] and fibrosis) that further increase the likelihood of delayed afterdepolarization and arrhythmia generation in response to localized sympathetic stimulation.[45,46]

Sympathetic stimulation also has effects on ionic currents that impact the ventricular action potential and risk for reentrant arrhythmias. The effects of adrenergic activation on individual ion channels have been reviewed elsewhere,[53,54] but one of the best known features of β-AR stimulation is an increase in L-type Ca^{2+} current via phosphorylation of the channel (Cav1.2).[55] This effect, by itself, is expected to increase APD, but is counterbalanced by the effect of β-AR on K^+ currents, most notably an increase in I_{Ks}, although I_{Kr} may also be involved.[56,57] The net effect of norepinephrine typically results in a shortening of the APD, a requirement for the heart to beat at faster rates during sympathetic activity. Because of the base-to-apex gradient in cardiac sympathetic nerves, however, sympathetic activation results in nonuniform changes in APD throughout the ventricle. For example, sympathetic nerve stimulation in a normal rabbit heart led to increased dispersion of repolarization and reversed the direction of the repolarization wavefront.[58] Administration of the β-AR agonist isoproterenol generated a different set of responses, suggesting that the dramatic changes in repolarization observed with sympathetic nerve stimulation were not because of differences in β-AR distribution or sensitivity, but rather because of the heterogeneous distribution of the nerves.[58] Similar results have been obtained in porcine ventricles, where dramatically different spatial patterns of activation-recovery intervals (surrogate measure for APD) and repolarization were observed in response to sympathetic nerve stimulation versus circulating norepinephrine.[59,60] Thus, even under nonpathological

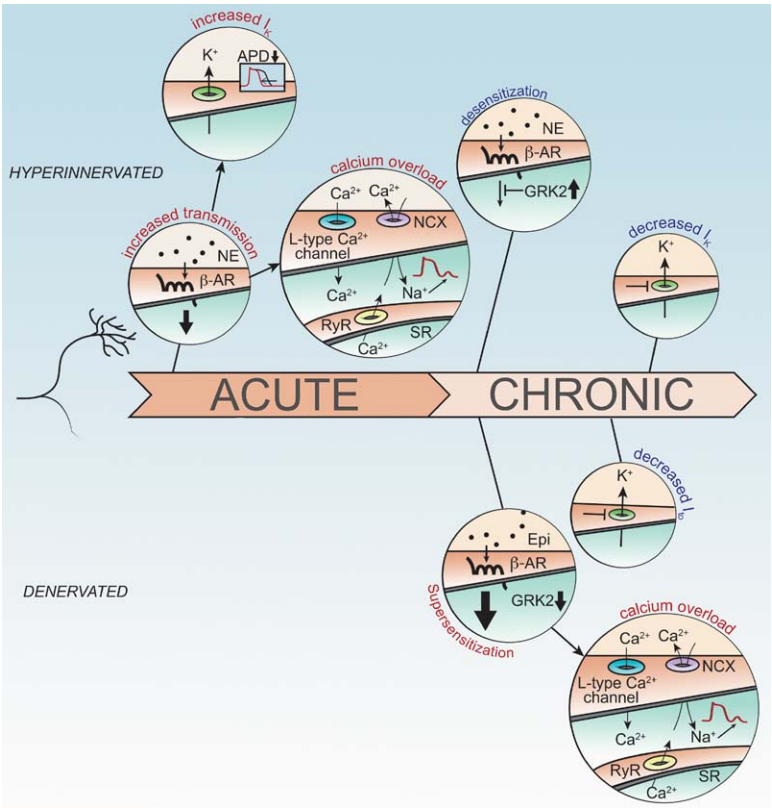

Figure 1. Hyperinnervation and denervation can both contribute to arrhythmias. Acute hyperinnervation or excess norepinephrine (NE; **top**) leads to increased activation of β-adrenergic receptors (β-ARs) and subsequent changes in I_k and calcium overload. β-AR signaling increases I_k, which shortens action potential duration (APD). At the same time, intracellular Ca^{2+} rises because of enhanced influx via the L-type Ca^{2+} channel and increased release from the sarcoplasmic reticulum (SR). Extrusion of Ca^{2+} from the cytosol via the Na^+/Ca^{2+} exchanger (NCX) produces a net inward current leading to delayed afterdepolarizations (DADs). In contrast, chronic hyperinnervation leads to desensitization of β-AR signaling and decreased I_k. Chronic denervation (**bottom**) results in β-AR supersensitivity and decreased I_{to}. Activation of supersensitive β-AR signaling pathways by circulating epinephrine leads to calcium overload and DADs.

conditions, considerable heterogeneity of sympathetic nerve distribution leads to increased dispersion of repolarization and potential for re-entrant arrhythmias. Therefore, in conditions of maladaptive nerve remodeling, significantly greater heterogeneity of APD and repolarization may exist. Indeed, sympathetic stimulation after MI not only caused increased dispersion of repolarization when compared with controls, but activation and propagation patterns were also altered significantly.[61] This was confirmed in patients with MI in whom reflex sympathetic stimulation caused a 230% increase in dispersion of repolarization when compared with patients with structurally normal hearts.[62]

Myocardial Responses to Chronic Hyperinnervation/Excess Norepinephrine

Acute effects of sympathetic activation often occur on a background of remodeled myocardial properties induced by heart failure or MI, but alterations to sympathetic transmission can also lead to chronic remodeling of the myocardium. Sympathetic hyperinnervation and elevated sympathetic tone are key features of many cardiovascular diseases. In these conditions, the myocardium becomes less responsive to adrenergic stimulation over time, and simultaneously less capable of maintaining adequate cardiac output, which further increases sympathetic drive from the central nervous system. The loss of cardiomyocyte responsiveness to adrenergic stimulation is a hallmark of sustained adrenergic stimulation and hyperinnervation.[63] Several factors contribute to this loss of sensitivity, including downregulation of the receptor itself,[64] but an especially important regulator of β-AR activity is the G-protein receptor kinase 2 (GRK2, also known as βARK1). Acutely, GRK2 is activated by protein kinase A in response to adrenergic stimulation and acts to inhibit β-AR activity in a self-contained negative feedback loop. Sustained activation of β-AR in adult mice, however, leads to increased GRK2 expression.[64] A similar increase in GRK2 is seen in canine heart failure, where it is reversed by sympathetic denervation, confirming regulation of GRK2 by sympathetic transmission.[65] Long-term activation of β-AR also leads to G-protein uncoupling and a reduction of Gαs protein,[66] as well as a reduction of repolarizing K^+ current.[67,68] Thus, sustained activation of ARs leads to adaptations that limit myocyte sensitivity to adrenergic stimulation and alter ion channel expression. Long-term treatment with β-blockers blunts many of these adaptations[63] and normalizes myocyte calcium handling,[69] contributing to the well-established protective effects of sympathetic blockade.[1–4]

Cardiac Denervation and Axon Degeneration

The mechanisms by which too much sympathetic transmission can be toxic for the heart are well characterized, but the local loss of sympathetic transmission within the heart also contributes to rhythm instability. Regional deficits in sympathetic transmission, identified in patients by imaging the uptake of labeled norepinephrine transporter substrates, have been observed in several pathological conditions including MI,[70,71] heart failure,[72] and Parkinson disease.[73] Several recent clinical studies suggest that sympathetic denervation after MI predicts the probability of serious ventricular arrhythmias,[74–76] and a detailed electric mapping study in human hearts revealed that sympathetic denervation of the normal myocardium adjacent to the scar resulted in β-AR agonist

supersensitivity and increased dispersion of repolarization that was arrhythmogenic.[62]

Paradoxically, members of the neurotrophin family of growth factors can be involved in the destruction of sympathetic nerves after cardiac injury. Although the neurotrophin NGF stimulates TrkA in sympathetic neurons to promote axon maintenance and process outgrowth, its precursor protein pro-NGF, which is elevated in the human heart after MI,[77] activates the p75 neurotrophin receptor (p75NTR, also called tumor necrosis factor receptor super family 16, TNFRS16), to trigger axon degeneration[78,79] (Figure 2). Similarly, pro–brain-derived neurotrophic factor and brain-derived neurotrophic factor selectively activate p75NTR on sympathetic neurons to stimulate axon degeneration.[80] The Trk tyrosine kinase receptors and p75NTR have opposing actions not only in cardiac sympathetic nerves[81] but also in the coronary vasculature[77] and cardiac myocytes.[15,82] Thus, pro-NGF activation of p75NTR after MI leads to the loss of nerve fibers in viable myocardium,[81] as well as microvascular damage and scar extension.[77]

Although activation of p75NTR can contribute to the loss of cardiac nerves, other factors are involved in sustaining denervation. Chondroitin sulfate proteoglycans are produced in the cardiac scar after ischemia-reperfusion, where they prevent reinnervation of the border zone and scar.[83] This contrasts with the scar that forms after sustained ischemia, which is devoid of chondroitin sulfate proteoglycans[83] and receives sympathetic hyperinnervation.[10,27] Removing or inhibiting the chondroitin sulfate proteoglycan receptor protein tyrosine phosphatase receptor σ in mice leads to reinnervation of the scar and border zone, restoring normal norepinephrine content and β-AR responsiveness to that region of the damaged left ventricle.[84] Consistent with the human studies linking post-MI denervation to arrhythmia risk, restoring innervation throughout the scar and border zone in mouse heart normalizes post-MI calcium handling and decreases arrhythmia susceptibility.[84]

Myocardial Responses to Chronic Denervation

Just as sympathetic hyperinnervation can alter the molecular makeup of myocytes, sustained sympathetic denervation has similarly profound effects. One of the best characterized changes is a loss of the transient outward K^+ current I_{to}, which is responsible for the initial repolarization in phase 1 of the action potential. Sympathetic denervation in rat decreases I_{to} by lowering expression of several different K^+ channel subunits and increases susceptibility to ventricular fibrillation.[85,86] Decreased I_{to} is also observed in disease states characterized by sympathetic denervation including Chagas disease, diabetic neuropathy, and MI.[84,87,88] Restoring adrenergic transmission in Chagas animals with norepinephrine infusion[89] or promoting sympathetic reinnervation of denervated infarct and border zone tissue[84] reverses the loss of I_{to}.

The consequences of sympathetic denervation are not limited to the transient outward K^+ current. Although hyperinnervation increases GRK2, sustained treatment with the β-blocker atenolol in mice[90] and surgical sympathectomy in dogs[65] leads to GRK2 downregulation. This reduction in GRK2 may play an important role in the β-AR supersensitivity observed after sympathetic denervation because GRK2 knockout mice exhibit a similar supersensitivity.[91] The absence of GRK2 also alters Ca^{2+} homeostasis by reducing (SR) Ca^{2+}-ATPase activity, which leads to reduced SR Ca^{2+} load and increased cytosolic Ca^{2+} levels, thus increasing NCX activity.[91] Increased activity of the electrogenic NCX can initiate delayed afterdepolarization, and the adrenergic supersensitivity that accompanies decreased GRK2 increases the likelihood that β-AR stimulation will be sufficient to overcome source–sink mismatch and generate focal arrhythmia.[47] Consistent with this possibility, isoproterenol stimulation of hearts after MI triggers focal arrhythmias that arise from denervated tissue near the infarct, whereas release of norepinephrine from sympathetic nerves in the same hearts does not trigger arrhythmias.[84] Restoration of sympathetic innervation to the scar and border zone of infarcted hearts prevents isoproterenol-induced arrhythmias and abnormal Ca^{2+} handling, confirming a role for denervation-induced β-AR supersensitivity in arrhythmia generation.[84] Sudden cardiac death is most common in the morning[92] when circulating catecholamines are rising rapidly,[93] suggesting that high circulating norepinephrine and epinephrine trigger arrhythmias in denervated myocardium via activating supersensitive β-AR signaling pathways. Thus,

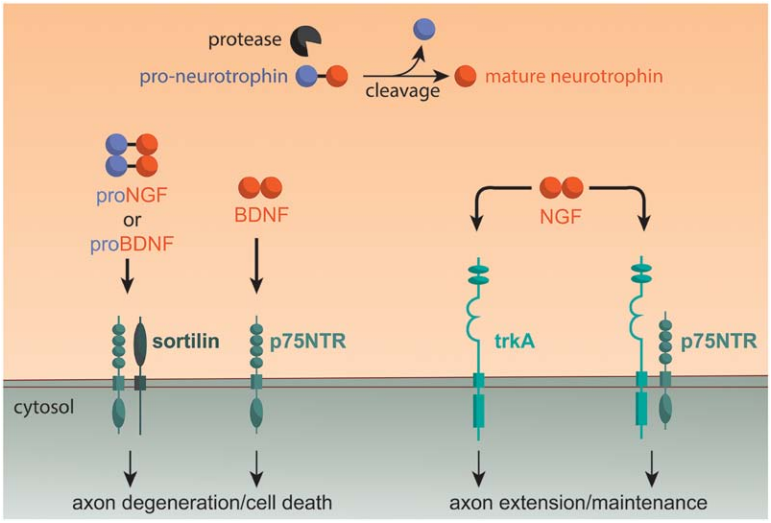

Figure 2. Neurotrophins stimulate different effects in sympathetic neurons via activation of p75NTR and tropomyosin related kinase A (TrkA). Pro-neurotrophins–like pro–nerve growth factor (NGF) and pro–brain-derived neurotrophic factor (BDNF) are processed to mature neurotrophins by intra- and extracellular proteases. Activation of a p75NTR/sortilin receptor complex by pro-NGF or pro-BDNF, or activation of p75NTR by BDNF, stimulates axon degeneration in sympathetic neurons. In contrast, NGF signaling via TrkA or a TrkA/p75NTR receptor complex stimulates sympathetic axon maintenance and growth.

denervation and hyperinnervation may trigger arrhythmias via similar mechanisms within cardiac myocytes.

Neurotransmitter and Neuropeptide Production

In addition to the loss or gain of nerve fibers, sympathetic neurons innervating the heart can undergo changes in neurotransmitter and peptide production and release after injury. Sympathetic nerves in the heart produce the peptide cotransmitter neuropeptide Y (NPY), which inhibits release of acetylcholine from cardiac parasympathetic nerves[94] and causes vasoconstriction on the cardiac vasculature.[95] NPY is elevated after MI,[96] and high plasma NPY levels in patients with acute ST-segment–elevation MI correlate with increased microvascular resistance after reperfusion.[97] NPY is released during periods of high sympathetic drive, and in the context of MI high levels of sympathetic activation resulting in NPY release seems to be detrimental for the heart. Over a longer time frame, cardiac damage can lead to changes in neuropeptide and neurotransmitter expression in sympathetic neurons. The best characterized change in sympathetic transmission is a developmental transition from production of norepinephrine to acetylcholine because of the actions of gp130 cytokines.[98] Recent studies revealed a similar change in phenotype triggered by cytokines such as leukemia inhibitory factor and cardiotrophin-1 during heart failure.[99] Stellate ganglia obtained from humans with heart failure also exhibited expression of proteins associated with cholinergic transmission,[99] suggesting that cholinergic sympathetic transmission can occur in the human heart. Although the functional consequences of acetylcholine release from sympathetic nerves are unclear, norepinephrine and acetylcholine have opposing effects on ventricular APD (norepinephrine shortens, whereas acetylcholine lengthens). Thus, cholinergic sympathetic transmission may indeed be arrhythmogenic by limiting the adaptation of the APD to increased heart rates during sympathetic activity. Therefore, the functional impact of changes in neurotransmitter phenotype represents an important area for future investigation.

Summary

Interactions between sympathetic neurons and cardiac myocytes can become destructive in pathophysiological conditions, giving rise to electric instability and increased arrhythmia susceptibility. We have summarized the most common changes that occur in cardiac sympathetic neurons during pathologies associated with increased ventricular arrhythmia risk, and how altered neurotransmission might contribute to arrhythmia generation. Many relevant studies were excluded because of reference limits, but we have tried to cite work from different laboratories who have contributed to our understanding. Interventions that target the sympathetic innervation of the heart have been successful in treating arrhythmias, and our hope is that this review will stimulate the development of new interventions aimed at normalizing sympathetic dysfunction.

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Disclosures

None.

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