Review Article

Adrenaline and the Heart: Physiology, a History, and Clinical Implications

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ABSTRACT

The fight-or-flight response triggers rapid-acting cardiac effects to enhance survival by increasing heart rate and contractility. These effects arise from adrenaline's effect on calcium ion channels and preexisting electrical signaling in cardiac muscle. Literature exploring the adrenergic pathway is well-established, as it includes the discovery of the funny current in 1979 and the "calcium clock," both of which are altered contractile mechanisms in the myocardium that play a key role in the heart's automaticity, as well as the expanding knowledge of adrenaline's several molecular pathways in cardiac tissue in modern literature. Modern clinical applications of adrenaline include heart conditions such as atrial fibrillation and genetic arrhythmias like Long QT Syndrome, of which adrenaline is a major trigger. Major therapies for these cases, such as beta-blockers or Ivabradine, are widely used in modern medicine and relate to adrenaline's cardiac pathway. Ultimately, this review aims to consolidate the extensive history of cardiac-adrenergic signaling in literature to further potential usage of signaling-related therapies in a clinical setting for treatment of adrenaline-related heart conditions.

Keywords: Adrenaline, Funny Current; Fight-or-Flight; Electrophysiology; Calcium Channels; Cardiac Muscle

INTRODUCTION

The fight-or-flight response has been highly conserved in vertebrates for millions of years to increase the chance of survival in response to acute stressors in the environment (1,2). When the brain perceives a threat from sensory stimuli, the sympathetic nervous system is activated to prepare a rapid response. This includes adrenaline-initiated stimulation of skeletal and cardiac muscles, causing more forceful and rapid contractions, which significantly increases heart rate and contractility to facilitate a bodily reaction (1, 3-6).

Two key regulatory mechanisms underline this cardiac response: the voltage clock and the calcium clock. In a resting state, cardiac ion channels, protein channels located on the cellular membranes of the electrical fibers of the heart, exchange K+, Na+, and Ca2+ ions to trigger an action potential that causes the rhythmic contraction of the heart. This triggering is mainly self-regulated by the voltage clock and the calcium clock, which are responsible for maintaining the cyclic beating of the heart by regulating action potentials throughout heart muscle (2, 8, 9). They trigger diastolic depolarization, the transmission

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of action potentials in the heart's resting phase to trigger another heartbeat. The cyclic activation and deactivation of the standard K+ and Na+ membrane ion channels in the sinoatrial (SA) node, the primary center of pacemaking in the heart (10), define the voltage clock. This is caused by the refractory period after an action potential in the node. This refractory period causes the "funny current," returning the intracellular voltage to the firing threshold for another action potential. The funny current is unique to pacemaker cells, as standard motor neurons in the peripheral nervous system do not return to the firing threshold without another stimulus, instead returning to a resting potential, which is not truly present in the SA node(2, 8, 11). Hyperpolarization-activated cyclic nucleotide–gated (HCN) channels, a group of channels uniquely activated during hyperpolarization in pacemaker cells in the refractory period, are responsible for this lack of a resting potential. These cause the funny current by allowing an influx of K+ and Na+ cations from outside the cell immediately after a given action potential, and triggering the next action potential (8, 9, 11) (Figure 1).

In parallel, the calcium clock is regulated by the cyclic release of calcium ions from the sarcoplasmic reticulum of SA node cells, which triggers the mechanism for contraction in a muscle cell. This, in conjunction with the funny current, contributes to spontaneous depolarizations in SA node cells by regulating intracellular calcium levels, facilitating rhythmic pacemaking. After the SA node sends out the action potential, the myocardium contracts due to the electrical signal and pumps blood (8, 11).

During acute stress, pacemaking activity of the SA node is strongly regulated by the sympathetic nervous system, with the parasympathetic system playing a secondary role. Sympathetic stimulation triggers release of adrenaline and noradrenaline from the adrenal glands and efferent cardiac nerves (12), both of which serve to alter heart rate and contractility. Efferent sympathetic nerves affect the heart by increasing the rate of diastolic depolarization, thereby triggering action potentials in the SA node more quickly and thereby increasing heart rate (13). These nerves also increase the myocardium's contractility in the fight-or-flight response, further enhancing the standard function of the heart (13). The majority of sympathetic interaction with the heart occurs via adrenaline and noradrenaline (4, 6, 7, 13), which trigger L-type calcium channels in muscles to open through adrenergic receptors, causing Ca2+ ions to enter and depolarize the cardiac muscle, leading to contraction (1, 3, 14). These adrenaline-triggered channels are also present in skeletal muscle to initiate more effective voluntary responses to a stressor (3).

The pacemaking properties of the SA node and how they are affected by the sympathetic nervous system are fundamental in some of the underlying causes of various types of arrhythmia, and how stress can contribute to their development. This review aims to examine the advances in literature that outline the current understanding of the mechanisms of cardiac fight-or-flight response. It also aims to identify future research avenues in the topic, particularly the effects of adrenaline on calcium channels, and to explore the therapeutic implications of these mechanisms, such as in cases of stress-related arrhythmias. Although the effects of adrenaline on cardiac physiology have been studied for decades, the integration of electro-

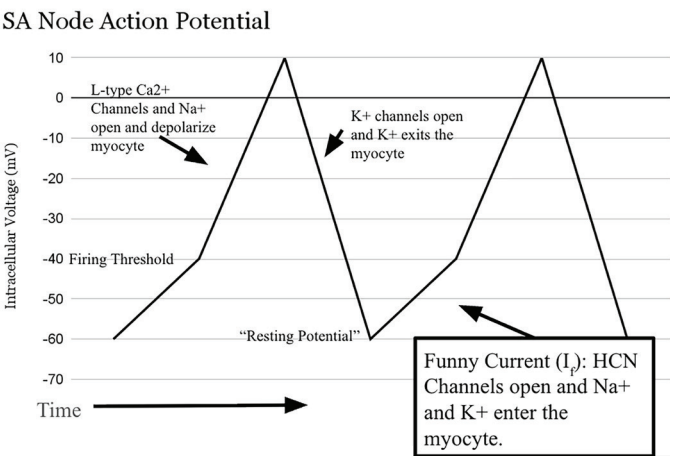

Figure 1. A basic, annotated action potential model of an SA Node. The intracellular voltage of the "resting potential" is ~ -60 mV, immediately being brought to the firing threshold by the funny current. The HCN Channel provides an influx of Na+ and K+ ions from the extracellular environment left over from the previous action potential. At ~ -40 mV, the firing threshold is reached, and voltage-gated Na+ channels and L-type Ca2+ channels open and provide an influx of Na+ and Ca2+ ions from outside of the cell. L-type calcium currents are modified by adrenaline to depolarize at a steeper slope than on the graph, letting in Ca2+ in a shorter amount of time, thus causing an accelerated heart rate (1,3,14). At ~ 10 mV, the L-type calcium channels close and K+ channels open to release intracellular K+ ions and repolarize the cell back to the resting potential, where the funny current begins another instance of contraction.

physiological mechanisms with clinical applica-tions in arrhythmia management remains fragmented, aside from the common use of beta-blockers. This review synthesizes current knowledge on adrenergic signaling, electrophysiological regulation, and therapeutic implications to potentially collect it in a manner that enables future clinical development.

HISTORY OF CARDIAC ADRENALINE

Discovery of the Funny Current

A particularly vital study on the relation between the heart and the fight-or-flight response was the 1979 discovery of the funny current conducted by Brown *et al*. In the study, they examined rabbit SA nodes and the effect that adrenaline had on them using a voltage clamp (6, 8). A major finding was the discovery of the funny current and its role in diastolic depolarization. Additionally, the researchers inferred that the cause of the increased heart rate in the fight-or-flight response was adrenaline accelerating the speed of the funny current (6, 8). This was seemingly at odds with the classical interpretation that described pacemaking as being caused by the deactivation of an outward current in the Purkinje fibers, a bundle of cells between the ventricles of the heart that assist in depolarizing the ventricles during the systolic phase (15). Further research into the funny current led to a new interpretation of an existing current in the Purkinje fibers, which was previously believed to be an outward current whose deactivation would stimulate pacemaking (8). Dario DiFrancesco, one of the key authors of Brown *et al*. 1979, posited in a 1981 study that the Purkinje current was an altered form of the funny current that was discovered two years earlier (8, 16).

Chronotropy and Inotropy

Links between adrenaline and increased heart rate were further developed in the late 1970s and 1980s. By analyzing action potentials in calf and cat hearts after exposure to adrenaline, Beresewicz and Reuter, in a 1977 study, examined the effects of adrenaline on cardiac action potentials. It was determined that adrenaline is responsible for enhancing L-type calcium currents and accelerating the calcium clock, which aids in pacemaking (17). This further adds to the varied list of mechanisms that adrenaline employs to increase the heart rate. Furthermore, Hoh *et al*. conducted a 1988 study regarding the effects of adrenaline on the rate of cross-bridge cycles in rat cardiac muscle. Cross-bridge cycles are the binding of myosin and actin protein filaments on a molecular level that facilitates muscle contraction (18). It was concluded that adrenaline significantly increases the contractile force and the contractile rate of these cross-bridge cycles via a beta-receptor-mediated mechanism (19). This was discovered through the use of propranolol, a beta-blocker that blocks beta receptors and antagonizes the mechanism of adrenaline on the rat hearts that were tested. Hoh *et al*. concluded that adrenaline more completely activates contractile proteins, increasing force as well as heart rate. (19)

Molecular Pathways of Adrenaline

Furthering both claims in a 1999 study, in a method similar to the one conducted by Bereswicz and Reuter but instead involving amphibian cells, Ju and Allen found that beta-adrenergic stimulation via adrenaline increased both action potential firing rate and the amplitude of the rate of Ca2+ release from the SR in frog cardiac cells (20). The increased rate of Ca2+ release provides a plausible mechanism for the increase in cross-bridge cycles, as cross-bridge cycles are triggered by Ca2+ binding to actin filaments in skeletal and cardiac muscle. What was still relatively unknown, however, was how exactly the adrenaline increased the rate of Ca2+ release on a molecular level. This concept would later be expanded upon in a 2003 study by Hulme *et al*., which posits that cAMP-dependent protein kinase A (PKA), a versatile enzyme that acts as a phosphorylation agent on receptors throughout the body (21), is the primary phosphorylation agent in L-type calcium channels in cardiac muscle. This was done using rat cardiac muscle and isoproterenol, a synthetic analog of adrenaline. Adrenaline first binds to an adrenergic receptor to generate cyclic adenosine monophosphate (cAMP), which stimulates PKA already present to enter a more active state (22), attaches to a calcium channel via A kinase anchoring protein 15 (AKAP15), which acts as a scaffold for PKA, allowing it to bind to the calcium channel to trigger the adrenaline-related changes. Hulme *et al*. removed a key element of AKAP15, a leucine zipper, that facilitated its binding to the calcium channel. Without the zipper, isoproterenol could not trigger any noticeable changes in the muscle, as it could not complete the signaling pathway involved with PKA (23), thereby proving the role of PKA in adrenaline's cardiac pathway.

The collective research done on myocardium involving adrenaline's pathway suggests that adrenaline

has a relatively consistent effect and mechanism on hearts across a wide variety of vertebrate species, highlighting its necessity and effectiveness in mechanism. Adrenaline consistently appears to bind to an adrenergic receptor on cardiac membranes (1, 3, 4, 6, 7, 9, 17, 19, 21, 22), then trigger the signaling pathway involving cAMP and PKA (22, 23), increasing the normal rate of intracellular Ca2+ release from the SR (20), thereby speeding up the calcium clock, which contributes to a higher heart rate. Adrenaline's effects include more completely activating contractile proteins (19) and quickening the action potential rate by increasing the speed of the funny current (6, 13, 16), all of which demonstrate adrenaline's force-increasing, or inotropic, and rate-increasing, or chronotropic, effects on cardiac muscle. Adrenaline also improves skeletal muscle contractility (3), improving the effectiveness of voluntary stress responses in addition to its chronotropic and inotropic effects.

MEDICAL APPLICATIONS

Spontaneous Arrhythmias

Medically, adrenaline's cardiac response is most commonly applied in cases of atrial fibrillation (AF), arrhythmias in the atria, which can affect a wide variety of patients and potentially can lead to heart failure (24). Their risk can be heightened by a multitude of factors, such as advanced age, increased alcohol consumption, and underlying heart disease, among others (24). A key trigger that can spontaneously cause an episode of AF in individuals at risk is psychological or physical stress (25), both of which are accompanied by the release of adrenaline in the body (26). Many patients with preexisting heart conditions experience AF during the daytime when triggered by exercise or emotional distress (25, 27). It has been demonstrated that these effects, typically induced by natural stress, can be reproduced by administering beta-adrenergic agonists, such as adrenaline (25, 28), suggesting their role in stress-related arrhythmias. Beta-adrenergic agonists such as adrenaline decrease the atrial effective refractory period (AERP) and increase the duration of the action potential generated by the SA node, putting increased stress on the atria and lengthening the time period where an AF episode may occur (25). Pharmacological treatments that help mitigate the effects of adrenaline usually come in the form of beta-blockers such as propranolol or nadolol, which dampen the effects of the fight-or-flight response by acting as antagonists to adrenaline and binding to beta-adrenergic receptors in the heart (25, 29). These reduce the overall effect that stress can have on those who suffer from chronic AF by reducing adrenaline's ability to cause an episode.

Genetic Arrhythmias

Alternative common medical applications are conditions related to genetic arrhythmias. These include long QT syndrome (30, 31), short QT syndrome (30), Brugada syndrome (30, 32), and more. All mentioned conditions mutate the ion channels within the cardiac conduction system. For example, the vast majority of long QT syndrome cases are caused by a mutation of the KCNQ1 and KCNH2 genes (30), which encode for the potassium channels in the myocardium. Defective potassium channels can lead to issues with repolarization, which tend to occur more often with a quickened funny current due to adrenaline (30) (Table 1). Various ion channel mutations, similar to the mutations characteristic of long QT syndrome, lead to symptoms of all three diseases including repeated episodes of tachycardia, a dangerously quickened heart rate, which is commonly over 150 beats per minute. Adrenaline, due to its chronotropic effects on ion channels in cardiac muscle, tends to trigger episodes of torsades de pointes, a specific form of potentially fatal tachycardia, by simulating electrophysiological conditions similar to those of torsades de pointes (33). In a similar vein to cases of AF, beta-blockers reduce the likelihood of an episode of torsades de pointes (34) by dampening the chronotropic effect that adrenaline has on cardiac muscle. Therefore, beta-blockers serve as an effective treatment for arrhythmic patients with tachycardic episodes (30, 35). In patients with Brugada syndrome, however, adrenaline and other beta-adrenergic agonists are an effective treatment due to the inward Ca2+ current in the cardiac action potential being diminished, causing episodes of arrhythmia due to an increase in depolarization time (32). Adrenaline increases the slope of the inward Ca2+ current, decreasing the likelihood of an episode (1, 3, 14, 32), while beta-blockers prevent this effect, leaving patients vulnerable to bouts of syncope and arrhythmia. Thus, isoproterenol is an effective treatment for Brugada syndrome (32) (Tables 1 and 2).

Although beta-blockers often are the first line of treatment, they can inadvertently reduce cardiac contractility and blood pressure since they completely block all of adrenaline's effects on cardiac muscle,

Table 1. Adrenaline-Related Conditions

Condition	Mechanism
Atrial Fibrillation	Any arrhythmia of the atria causing episodes of tachycardia and irregular blood flow. Adrenaline decreases the duration of the atrial effective refractory period, the period in which another action potential cannot be fired, and increases the duration and intensity of a contraction generated by the SA node. This increases the likelihood of an episode of AF, as the atria are under increased stress and have more potential triggers of an episode with the decreased refractory period.
Long QT Syndrome	Mutations of the KCNQ1 and KCNH2 genes, which encode for K+ channels in the myocardium. Long QT syndrome lengthens the repolarization phase of the cardiac action potential, reducing the outward flow of K+ ions in the SA node. Adrenaline, accelerating the funny current, causes arrhythmia and episodes of torsades de pointes in conjunction with the reduced K+ flow, due to the duration of one phase of the action potential being increased by Long QT syndrome, while adrenaline reduces the duration of another via its chronotropic effects.
Short QT Syndrome	Commonly mutations of the KCNQ1 and KCNH2 genes, which encode for K+ channels in the myocardium. Short QT syndrome shortens the repolarization phase of the cardiac action potential, increasing the outward flow of K+ ions in the SA node. Adrenaline, accelerating the funny current, causes arrhythmia and tachycardic episodes in conjunction with the increased K+ flow, due to the combined reduction of two phases of the action potential, increasing heart rate to an irregular state.
Brugada Syndrome	A genetic mutation of the L-type Ca2+ channel inhibits the intracellular flow of Ca2+ ions during SA node depolarization, reducing heart rate and causing episodes of syncope and arrhythmia due to a decrease in blood flow and irregularities in depolarization. Beta-blockers are not advised for treatment, as they further exacerbate the inhibition of Ca2+ flow and worsen symptoms. Isoproterenol and adrenaline are effective treatments due to their increase in Ca2+ flow, counteracting the prior inhibition.

which can be an issue if only a reduction in heart rate is required (29, 36). These include its inotropic effects (19), its chronotropic effects on the funny current (6, 13, 16), and Ca2+ release from the SR (20). In certain scenarios, such as in cases of arrhythmia, like AF or a congenital disease, this broader approach works to alleviate symptoms initially. Still, this can have numerous negative side effects, including hypotension, psychological depression, erectile dysfunction, and worsening of intrinsic atrioventricular node disease (37), especially in patients with abnormalities in the heart's conduction system (36). In many cases, such as in coronary artery obstruction (37), where the blood supply of the cardiac muscle itself is blocked (38), or in cases of AF following heart surgery (36), Ivabradine serves as a more effective treatment than beta-blockers. Ivabradine manipulates the HCN channels within the SA node (39), manipulating them to disrupt the flow of Na+ and K+ ions, achieving a "pure" decrease in heart rate by solely slowing the funny current, leaving muscle contractility and blood pressure unaffected (36, 37, 39, 40). This more targeted effect can be more helpful in patients who require their heart rate to be lowered without running the risk of lower blood pressure or heart weakness. The medication is specifically useful in assisting with angina, pain in the upper chest caused by a lack of blood flow to the coronary arteries (41), as by reducing the heart rate, Ivabradine generally reduces the amount of oxygen needed by cardiac muscles, reducing the likelihood of episodes of angina. As of now, the first line of medication involved in the treatment of arrhythmia continues to be beta-blockers, as has been the medical standard, but Ivabradine is now a valuable alternative in the case of patients at risk of low pressure or experiencing angina (42) (Table 2). What remains elusive is the medicines needed in cases of chronic stress. Beta-blockers and Ivabradine are effective at handling cases of short-term, episodic stress. Still, in cases of those who experience chronic anxiety and stress alongside a heart condition, the side effects of both medications can negatively impact patients, necessitating the research of more long-term medications.

CONCLUSION

The cardiac fight-or-flight response has not only been conserved for millions of years, but it has been

Table 2. Adrenaline-Related Medications

Medication	Mechanism	Treatments
Isoproterenol	Mimics the effects of adrenaline by interacting with beta-adrenergic receptors to achieve chronotropic and inotropic effects. Increases the intensity of the fight-or-flight response by increasing the slope of the inward Ca2+ current and the funny current, and more completely activates contractile proteins in the myocardium.	Brugada syndrome patients experience arrhythmias due to a decrease in the slope of the inward Ca2+ current, slowing depolarization of the heart, which leads to bouts of syncope. Isoproterenol counteracts this by increasing the slope of the Ca2+ current and funny current, achieving a positive chronotropic effect and reducing bouts of syncope due to increased blood flow.
Beta-Blockers	Antagonizes beta-adrenergic receptors in myocyte tissue, blocking adrenaline or noradrenaline from activating its pathway. This causes a reduction in intensity in adrenaline-initiated responses to an external stressor. Beta-blockers reduce heart rate by preventing the funny current from being accelerated by adrenaline, and muscular and cardiac contractility by preventing adrenaline's effect on contractile proteins. Beta-blockers additionally reduce blood pressure and alternate adrenaline-related effects across several systems.	Used as a medication for arrhythmias that present in acute episodes, such as Long QT Syndrome, AF, and Short QT Syndrome. The frequency of tachycardic episodes for patients with arrhythmia is exacerbated by adrenaline's chronotropic effects. Beta-blockers reduce and prevent adrenaline's effects, lowering heart rate and reducing the likelihood of an episode.
Ivabradine	Modulates HCN channels in the SA node to reduce the transmembrane flow of Na+ and K+ into the cell during the funny current. Thereby achieves a "pure" negative inotropic effect due to the reduction of flow, thus increasing the duration of the funny current, and thus solely lowering heart rate. Ivabradine seemingly has no inotropic effect.	Used as an alternative medication to beta-blockers, especially in patients with preexisting low blood pressure and cardiac weakness, or patients experiencing issues following cardiac surgery. Beta-blockers' negative inotropic effects can be detrimental to patients with said conditions, and Ivabradine avoids that due to its lack of inotropic effect entirely. It solely decreases heart rate, treating arrhythmia, while simultaneously leaving cardiac contractility and blood pressure unaffected.

conserved across a variety of vertebrate species, implicitly demonstrating its evolutionary value in an animal's response to a stressful environment (1, 2). It not only increases heart rate and contractility (3-6, 8, 15, 17, 19-21), but it also increases the contractility of skeletal muscles (3), providing the energy and strength needed in response to an immediate stressor. In a modern context, the fight-or-flight response often presents in the form of anxiety or stress, which can cause a variety of issues for those with preexisting heart conditions. These include arrhythmias, whether it be genetic or spontaneous (24–32), coronary heart obstruction (37, 38), and complications after cardiac surgery (36). The chronotropic and inotropic effects of the fight-or-flight response can prove to be overbearing in those cases, and therefore, treatments like beta-blockers or Ivabradine can assist in alleviating the effects of adrenaline on the funny current, calcium clock, and cardiac proteins in its pathway (18, 27, 29, 35–37, 39, 40).

Despite the major implications and mechanisms discussed, this review presents the cardiac adrenaline pathway in a more streamlined manner than what is currently known and documented in academia, emphasizing clarity and accessibility over comprehensiveness. More complex cardiac pathways involving adrenaline exist, the mechanisms of which are still yet to be fully researched, and more potential medical applications for adrenaline, beta-blockers, and Ivabradine exist, but this review is not fully comprehensive of those alternate pathways and applications, many of which are widespread in modern knowledge of the cardiac sympathetic response.

A major limitation in modern knowledge,

however, is the multitude of relative unknowns that are still present on the stage after adrenaline or noradrenaline binds to a beta-adrenergic receptor. While the pathways involving cAMP and PKA are well-documented (21–23), beta-adrenergic receptors also affect the myosin regulatory light chain (RLC) pathway (43), whose mechanisms are relatively elusive. This pathway is often altered in cardiac disease by making a sarcomere less sensitive to calcium, decreasing its contractility (44), so it is necessary to research any potential effects adrenaline could have on this pathway. It could open up a new avenue in cardiac medication that could further assist those who have altered RLC pathways, especially in cases of chronic heart failure and arrhythmias.

Thus, further dissecting adrenergic signaling at the molecular level may reveal novel targets for treating stress-induced arrhythmias and improve our understanding of autonomic regulation in health and disease. Research still needs to be done on the molecular mechanisms of adrenergic stimulation, including its effects on the RLC pathway, to develop more therapies for diseases that involve both pathways, such as hypertrophic or dilated cardiomyopathy (43, 44). Many biologists, such as Dario DiFrancesco (6, 8, 9, 16, 40) or Ohnuki *et al*. (43), are conducting vital avenues of this research. According to the Heart Rhythm Society, approximately 37.5 million people suffer from AF, with an estimated 60% increase in cases by 2050 (45). This research will enable more effective and efficient treatments and medications for AF, arrhythmias, and stress-related heart conditions on a larger scale. The knowledge gained will hopefully be of use to cardiologists, electrophysiologists, and neurologists, assisting more patients with adrenaline-related heart conditions on a global scale.

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CONFLICT OF INTERESTS

The author declares that there are no conflicts of interest regarding the publication of this article.

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