Pumped Up: A Review of Adrenaline and the Heart

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Abstract

The fight-or-flight response is commonly seen as an animal's immediate response to danger, causing a wide variety of physiological changes. Cardiac muscles contract more forcefully and quickly in the fight-or-flight response, and the mechanisms responsible for this shift in response mostly involve ion channels and electrical impulses in the heart. This paper will review these electrical mechanisms, primarily caused by adrenaline's effect on calcium ion channels, preexisting cardiac rhythms, and cardiac muscle tissue itself. A basic history of research involving said effects to better understand the interactions between adrenaline, calcium ion channels, and the cardiac muscles. This history includes the discovery of the funny current, advancements in understanding adrenaline's effects on the heart, and the expanding knowledge of adrenaline's molecular pathway in cardiac tissue. This review will also detail several medical applications of this understanding, including in cases of atrial fibrillation and genetic arrhythmias, and explore treatments such as beta-blockers or Ivabradine that relate to adrenaline's molecular pathway. Further research in this field that involves the molecular interaction of adrenaline with other pathways within cardiac muscle will be explored as well, hopefully to the benefit of those who suffer from cardiac disease. Ultimately, this review aims to analyze the applications of this research, its medical implications, and current research in the field of adrenaline to further our understanding of the cardiac fight-or-flight response.

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

Introduction

The fight-or-flight response is perhaps one of the most primal reactions to danger we have as humans. It is a highly conserved response in vertebrates, including us, for millions of years, to increase the chance of survival in a seemingly threatening situation[1,2]. Upon registering a threat, whether it be a predator in the wild, a sudden movement from someone else that causes you to jump, or even an upcoming presentation, our body enacts a series of physiological changes to respond to that threat. When the brain perceives a threat from sensory stimuli, our breathing rate increases, our eyes widen, and our muscles, whether it be skeletal or cardiac, start to contract more forcefully and quickly[3,4]. The mechanism for this shift in the response of the muscles varies depending on the type and location of the muscle. In the heart specifically, a shift in response is vital, as the heart is responsible for fueling muscles with blood, and more energy is required in the fight-or-flight response. The shift in function of cardiac muscles is controlled by calcium currents initiated by adrenaline, a hormone released by the adrenal medulla during the fight-or-flight response[5], that increase the beating rate in the heart, pumping blood to the muscles to facilitate fight or flight[1,3,5,6].

What ion channels are involved?

I. Voltage Clock

When not triggering the fight-or-flight response, the cardiac ion channels, which are protein channels located on the cellular membranes of the electrical fibers of the heart, exchange certain ions between the intracellular and extracellular environments. This exchange triggers an action potential, an electrical stimulation that travels across electrical fibers and stimulates muscle contraction and extension. The main mechanism behind the electrical impulses that cause heart muscles to contract is mainly self-regulated by the voltage clock and the calcium clock[2]. These clocks are responsible for maintaining the rhythmic beating of the heart via regulating action potentials throughout the heart muscle[2,8,9]. They help to trigger diastolic depolarization, the sending out 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 main center of pacemaking in the heart[10], are what 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," slowly bringing the cell back to the firing threshold for another action potential[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 reaction. These cause the funny current by allowing an influx of K+ and Na+ cations from outside the cell, and triggering the next action potential[8,9,11].

II. Calcium Clock

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 muscles of the heart, the myocardium, contract due to the electrical signal and pump blood[8,11].

What happens to the heart in the fight-or-flight response?

Within the fight-or-flight response, these pacemaking properties of the SA node are primarily regulated by the sympathetic nervous system, and also by the parasympathetic nervous system to an extent. When reacting to a potential threat in the environment, such as a predator, the sympathetic nervous system instigates the release of epinephrine/adrenaline and norepinephrine/noradrenaline via the adrenal glands on the kidneys, and directly impacts the heart via efferent cardiac nerves[12], both of which serve to help the body react to danger. These efferent sympathetic nerves influence the heart by increasing the speed of diastolic depolarization, triggering action potentials in the SA node more quickly and thus increasing heart rate[13]. These nerves also essentially galvanize the myocardium and increase its contractility in the fight-or-flight response, further stimulating the heart's ability to pump blood to the muscles of the body[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 via adrenergic receptors and cause Ca2+ ions to enter cardiac muscle, depolarizing the muscle and causing

contraction[1,3,14]. As stated previously, calcium ions are particularly potent when it comes to depolarization due to their charge, and therefore are an effective way for the heart to quickly increase its force and its beating rate in moments of danger. These adrenaline-triggered channels are also present in skeletal muscle as well[3], so that the body may physically fight back or run away faster and more powerfully in these moments compared to normal circumstances.

These mechanisms are vital components of one of the most conserved responses to stress in vertebrates, and they are important to our understanding of the heart's reaction to stress. The pacemaking properties of the SA node and how they are affected by the sympathetic nervous system are especially needed to understand some of the underlying causes of arrhythmia and how it can be caused by stress. Overall, this review aims to examine the advances in research that outline our current understanding of the mechanisms of cardiac fight-or-flight response. It also aims to identify future lanes of research in the topic, particularly the effects of adrenaline on calcium channels, and to explore the therapeutic avenues of these mechanisms, such as in cases of stress-related arrhythmia.

History of Cardiac Adrenaline

Discovery of the Funny Current

Perhaps the most vital study on the relation between the heart and the fight-or-flight response was Brown et al.'s 1979 discovery of the funny current. In the study, they examined rabbit SA nodes and the effect that adrenaline had on them via 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 in the phase of a heartbeat when pumping occurs[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 researchers in 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 examined in a seminal study in 1977 the effects of adrenaline on cardiac action potentials. It was determined that adrenaline is responsible for enhancing L-type calcium currents and quickening the calcium clock, which assists 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 crossbridge cycles in rat cardiac muscle. Crossbridge 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 crossbridge cycles via a beta receptor-mediated mechanism.[19] This was discovered through the use of propranolol, a beta-blocker that covers beta receptors and therefore blocks the mechanism of adrenaline on the rat hearts that were tested. Hoh et al. concluded that adrenaline more completely activates contractile proteins.[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 gives a plausible mechanism for the increase in crossbridge cycles, as crossbridge 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 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 to 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 of sorts 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 helped it bind 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], proving its role in the cardiac fight-or-flight response.

Summary of Discoveries

All of these seminal papers have demonstrated that adrenaline has a relatively consistent effect and mechanism on hearts across a wide variety of species, including rats, cow calves, cats, sheep, frogs, and likely us. This highlights the necessity of the fight-or-flight response as a defense mechanism through its conservation across many stages of evolution. 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 signalling pathway involving cAMP and PKA[22,23], increasing the normal rate of intracellular Ca2+ release from the SR[20], speeding up the calcium clock, contributing to a higher heart rate. Adrenaline also has a myriad of additional effects that increase the contractile force and rate of the heart. This includes more completely activating contractile proteins[19] and quickening the action potential rate by increasing the speed of the funny current [6,13,16], directly causing more heartbeats in a shorter period. All of these demonstrate adrenaline's force-increasing, or inotropic, and rate-increasing, or chronotropic, effects on cardiac muscle, increasing the heart's ability to pump blood throughout the body when it is most needed in a

stressful situation. Adrenaline also improves skeletal muscle contractility[3], making the impact of the “fight” or the “flight” much more powerful. By expanding the ability of cardiac and skeletal muscles, adrenaline plays a vital role in our ability to survive in a pinch, by energizing the body through the former and mobilizing the body in the latter.

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 shown that these effects, normally caused by natural stress, can be reproduced by applying beta-adrenergic agents like adrenaline[25,28], implicating its role in stress-related arrhythmia. 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 an antagonist to adrenaline and binding to beta-adrenergic receptors in the heart[29]. These can help to 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

Another common medical application is 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, leading to unexpected effects on the heartbeat. For example, symptoms of all three diseases include repeated episodes of tachycardia, a dangerously fast heart rate, often 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[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].

Although beta-blockers often are the first line of treatment, a disadvantage that the drugs can have is that they reduce cardiac contractility and blood pressure on top of lowering heart rate, since they completely block all of adrenaline’s effects on cardiac muscle[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], what would be more useful than beta-blockers is a drug called Ivabradine. Ivabradine manipulates the HCN channels within the SA node[39], inhibiting them to disrupt the flow of Na+ and K+ ions, achieving a sort of "pure" decrease in heart rate by solely slowing the funny current that controls heart rate, leaving muscle contractility and blood pressure unaffected[36,37,39,40]. This more targeted effect can be more helpful in patients who just need their heart rate lowered without running the risk of lower blood pressure or a weaker heart. The drug 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, helping to stave off 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]. 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, but in cases of those who experience chronic anxiety and stress alongside a heart condition, the side effects of both drugs can flare up, necessitating the research of more long-term medications.

Limitations

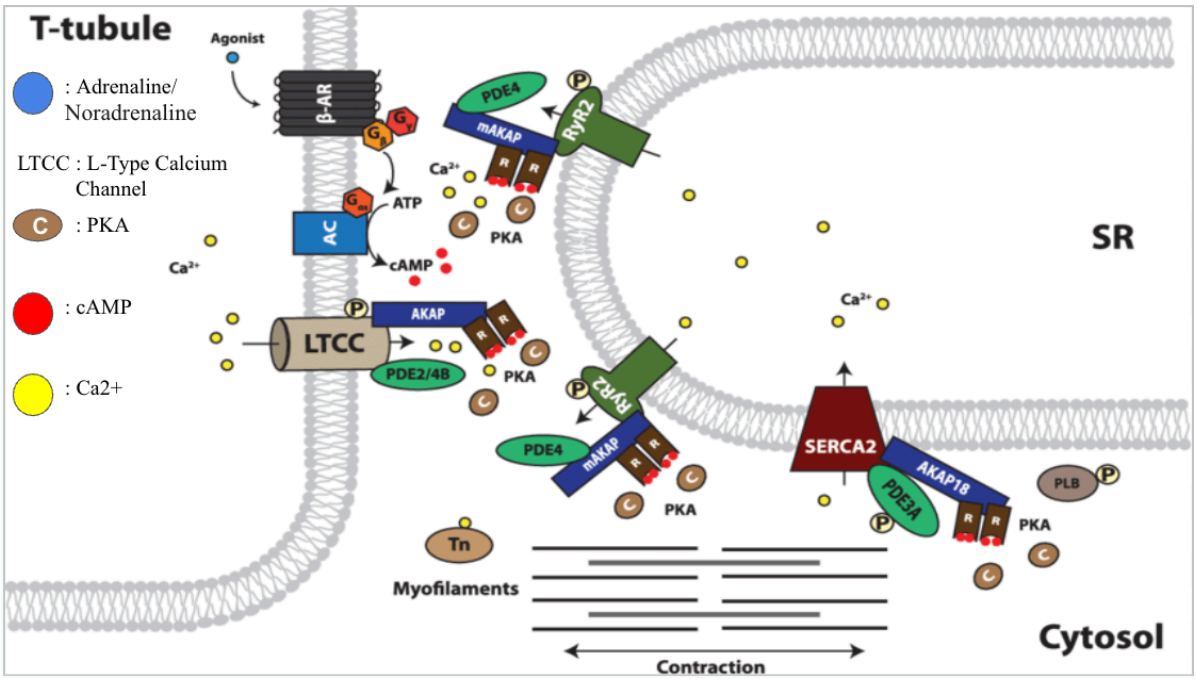

Figure 1

Caption: Modified Diagram of the Adrenaline/cAMP pathway in a cardiac muscle cell. Original diagram by Pallien and Klussmann[46]. This review's presentation of the adrenaline pathway is not as in-depth as the diagram. This review presents adrenaline and noradrenaline as being released in times of stress[47], then binding to a beta-adrenergic receptor on cardiac muscle. It then phosphorylates cAMP, which stimulates PKA to bind to a calcium channel[21–23], which alters the channel to speed up Ca2+ release from the SR. This simultaneously increases the speed of the funny current[6,13,16], and more completely activates contractile proteins[19]. The diagram includes several interactions that the review streamlines for clarity, such as the cAMP interaction with SERCA2.
Adapted from Pallien and Klussmann, Biochem Soc Trans, 2020.

Since Brown et al. discovered the funny current in 1979, much progress has been made in our understanding of adrenaline, the fight-or-flight response, and their effects on the heart. However, there are still several limitations that exist in this review, as well as in the general field that hinder our full understanding. The majority of studies done to examine the mechanism of action of adrenaline have been done on animals, like rabbits[6], cats[17], cows[17], rats[19,23], sheep[4], and frogs[20]. While the mechanism of the fight-or-flight response is highly conserved and similar in most of these cases, a full molecular analysis on humans is difficult due to the dependence on non-invasive procedures. Procedures involving biopsy are rarer than animal studies, due to the relative ease of using animal cardiac tissue for procedures involving adrenaline. If there were any practical differences in the adrenaline system unique to humans, they would be relatively lesser-known.

Another limitation 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 in a way that negatively impacts muscle contractility by making a sarcomere less sensitive to calcium[44], so it is important 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.

This review presents the cardiac adrenaline pathway in a more streamlined manner than what is currently known and documented in academia. Figure 1 demonstrates how the pathway is structured in this review. The way this pathway is described is much simpler than the full effect of adrenaline on cardiac muscle. More complex pathways like RLC 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.

Conclusion

The cardiac fight-or-flight response has not only been conserved for millions of years, but it has been kept across a variety of different species, whether it be mammal or amphibian, implicitly demonstrating its evolutionary value in an animal's response to a stressful situation[1,2]. It not only increases our heart rate and its contractile power[3–6,8,15,17,19, 20, 21], but it also increases the contractility of skeletal muscles[3], providing the energy and strength needed in a dire

situation. In a modern context, the fight-or-flight response that saved the lives of our ancestors and many others today often comes in the form of anxiety or stress from societal factors like upcoming deadlines or interpersonal relationships (https://pubmed.ncbi.nlm.nih.gov/39089322/, which can cause a variety of problems 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, drugs like beta-blockers or ivabradine can help to alleviate the effects of adrenaline[27,29,35–37,39,40]. However, 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 more of the molecular mechanisms of adrenergic stimulation, including its effects on the RLC pathway, to develop more therapies for diseases that involve both, like hypertrophic or dilated cardiomyopathy[43,44]. Many biologists, such as Dario DiFrancesco[6,8,9,16,40] or Ohnuki et al.[43], are spearheading research on adrenaline and the funny current to this day. According to the Heart Rhythm Society, approximately 37.5 million people suffer from AF alone, 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, helping to benefit more people with adrenaline-related heart conditions worldwide.

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