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Review Article

Heart's Signaling Symphony: Exploring Cardiac Receptors

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Abstract: This overview delves into the intricate interplay between adrenergic and cholinergic receptors in regulating heart function. The sympathetic and parasympathetic nervous systems play a powerful role in controlling cardiac function by activating adrenergic and muscarinic receptors. In the human heart, there exist α_1, β_1, and β_2- adrenoceptors and M_2-muscarinic receptors and possibly also (prejunctional) α_2-adrenoceptors. The human heart has a very uniform distribution of β_1 and β_2-adrenoceptors and a heterogeneous distribution of M_2-receptors (more receptors in the atria than the ventricles). Heart rate and contraction force increase whenever β_1 and β_2-adrenoceptors are stimulated, while heart rate and contraction force fall when M_2 receptors are stimulated (directly in the atria and indirectly in the ventricles). The distribution of β_1 and β_2-adrenoceptors in the human heart can be changed by pathological conditions (like heart failure) or pharmacological interventions (like -blocker medication), nevertheless, M_2-receptors are much less influenced. The intricate relationships between these receptor systems offer possible cardiovascular disease therapy strategies. More research must be conducted, focused on the complex control mechanisms that regulate cardiac function and pathology, to fully comprehend the subtleties of these signalling pathways and how they affect heart health.

Keywords: Cardiac myocytes, Cardiac receptors, Chronotropic effects, Inotropic effects, Transduction pathways, and Signalling pathways.

INTRODUCTION

Numerous receptor systems in cardiac myocytes regulate heart rate and contractility (Brodde *et al.*, 2001). The autonomic nervous system, which includes the sympathetic and parasympathetic nervous systems that interact with adrenergic and cholinergic receptors is the most important mechanism regulating cardiac function. Multiple subtypes of adrenoceptors and cholinergic receptors exist, and these receptor subtypes can also be found in the cardiac myocytes (Timothy DO Connell *et al.*, 2014). Variations in the pressure within the cardiac chambers trigger the activation of three distinct groups of receptors within the heart. These receptors are widely distributed throughout the body. The central nervous system (CNS) functions through muscarinic cholinergic and adrenergic receptors, which operate based on the same pharmacological principles.

Adrenergic, muscarinic, and cholinergic receptors are members of a much wider superfamily of G protein-coupled receptors that share a common mechanism of signal transduction, according to research on the receptors using molecular biology. Large unencapsulated nerve endings in one group are grouped at the points where the pulmonary veins and the left atrium come together, as well as the caval veins and the right atrium. Myelinated afferent vagal nerves that conduct at 8 to 32 m/s innervate these cardiac receptors. Unmyelinated afferent vagal nerves (C fibers) that conduct at velocities of 2.5 m/s or less provide a second group. The pericardial, epicardial, interstitial and perivascular tissues contain these tiny nerve fibers, which are a part of the myocardium's extensive innervation. However, this network of fibers has no known endpoints. The so-called sympathetic afferent nerves are a third class of receptors found throughout the heart's chambers and contain both myelinated and unmyelinated afferent nerves accompanying sympathetic nerves on their way to the spinal cord. The primary focus of this article is the types, presence, distribution, and physiological function of adrenergic,

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cholinergic, and other receptor subtypes in cardiac myocytes and blood vessel cells.

ADRENERGIC RECEPTORS IN THE HUMAN HEART

Adrenergic receptors (ARs) bind to and are stimulated by the endogenous catecholamines epinephrine and norepinephrine (NE). Whereas norepinephrine is synthesized in sympathetic nerve terminals in the brain and peripheral nervous system, epinephrine is mainly produced in the adrenal gland and distributed into the bloodstream. The two primary ARs in the heart are the β-ARs, which make up around 90% of all cardiac ARs, and the α_1-ARs, which comprise around 10% (Faure C *et al.*, 1995).

α_1-ADRENOCEPTORS

Presently, three distinct α_1-adrenoceptor subtypes have been identified and pharmacologically characterized; they are known as α_{1A}, α_{1B}, and α_{1D}. Studies on reverse transcription polymerase chain reaction (RT-PCR), and RNase protection assays indicate the presence of α_1 adrenoceptors at the mRNA level, protein level, and in the human heart. All studies affirm that the most prevalent α_1 adrenoceptor subtype in the human heart at the mRNA level is the α_{1A}-adrenoceptor (Brodde OE *et al*,1978). Several groups have used Radio ligand binding investigations to demonstrate the existence of α_1-adrenoceptors on a protein level in the human heart's left and right ventricles; nevertheless, their density is considerably lower than that of β-adrenoceptors. Early research on the signal transduction pathways after α_1-adrenoceptor stimulation had demonstrated that the α_1-adrenoceptors do not raise cyclic AMP, indicating that the Gs/adenylyl cyclase/cyclic AMP system is not involved in research (Jahnel U *et al*,1992). It is now clear that the primary mechanism by which α_1-adrenoceptors couple to the phospholipase C/inositol trisphosphate/diacylglycerol (PLC/IP_3/DAG) system is through a PTX-insensitive G-protein (G_q/11) **(Figure 1).**

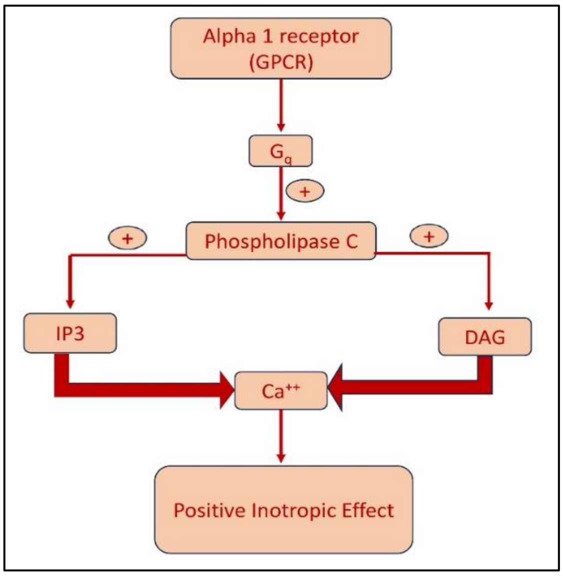

Figure 1: The Gq type of alpha-1 receptor activates phospholipase C, raises IP_3 and DAG, and eventually raises intracellular calcium concentrations, which causes muscle contraction

Furthermore, noradrenaline stimulated α_1-adrenoceptors in human ventricular tissue and the human right atrium to produce higher inositol phosphates. This has also been shown to occur in the human heart. Positive inotropic effects in the human heart are induced by α_1-adrenoceptor activation (Halfdan Aass *et al.*,1986). However, the maximal inotropic effect was only 15–35 % of that generated by β-adrenoceptor stimulation. Therefore, positive inotropic effects could be demonstrated in human atrial and ventricular preparations by using phenylephrine in the presence of β-adrenoceptor antagonists (Schafer M *et al.*, 2001). Increased IP_3-formation may facilitate the release of Ca^{2+} from intracellular reserves, which may contribute to increases in contraction force, and this is the mechanism underlying the positive inotropic effect generated by α_1-adrenoceptor activation. Moreover, it has been proposed that activation of the Na^+/H^+ exchanger causes intracellular alkalinization through increased Ca^{2+} sensitivity of myofilaments and trans sarcolemmal Ca^{2+} influx and that DAG-induced activation of protein kinase C is responsible for at least some of these effects. Extended stimulation of cardiac α_1-adrenoceptors can lead to the formation of a hypertrophic phenotype in addition to increases in contractile force. This has been observed in isolated cardiomyocytes from adult rats or even in vivo animals. It has also been shown in isolated cardiomyocytes from young rats. According to recent studies, α_{1A}-adrenoceptor stimulation mainly leads to the hypertrophic response in adult rat cardiomyocytes (measured by [3H] phenylalanine incorporation into the cardiomyocytes), whereas β_1-adrenoceptor stimulation inhibits the hypertrophic response (Durkee CA *et al.*, 2019).

α_2-ADRENOCEPTORS

The alpha-2 (α2) adrenergic receptor (or adrenoceptor) is a G protein-coupled receptor (GPCR) that is connected with the G_i heterotrimeric G-protein. It is made up of three adrenergic subtypes α_{2A}, α_{2B}, and α_{2C} that are extremely close to one another. A fourth α_{2D} adrenergic receptor is also expressed by several non-human species. While some research has shown the existence of α_2-adrenoceptor subtypes in the human heart at the mRNA level by RT-PCR or RNase protection experiments, many groups have not been able to demonstrate α_2-adrenoceptors at the protein level. Catecholamines such as norepinephrine (noradrenaline) and epinephrine (adrenaline) communicate with the central and peripheral nervous systems via the α_2-adrenergic receptor. However, in functional studies, multiple groups have shown that presynaptic α_2-adrenoceptors exist and mediate the suppression of noradrenaline release in the human right atrium. By inhibiting adenylyl cyclase, the α_2 receptor functions as an allosteric inhibitor, reducing the production of intracellular cAMP **(Figure 2)**. Moreover, it results in less cytoplasmic calcium, which decreases the release of neurotransmitters and central vasodilation (Joseph Zacharia *et al.*, 2004).

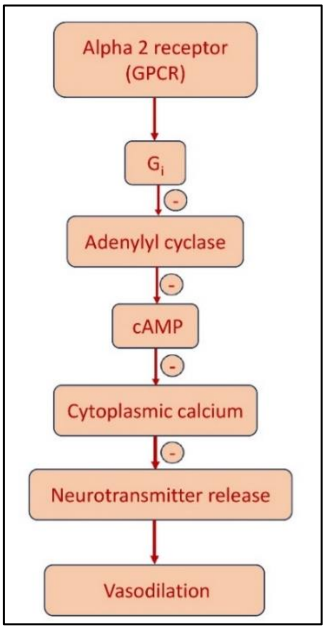

Figure 2: Through the G_i function, the alpha-2 receptor functions as an allosteric inhibitor, inhibiting adenylyl cyclase and reducing the production of intracellular cAMP. It results in less cytoplasmic calcium, reduced neurotransmitter release and central vasodilation

β-ADRENOCEPTORS

As of now, three distinct β-adrenoceptor subtypes known as β1, β2, and β3 have been cloned and pharmacologically identified (Maria TM *et al.*, 2021). It is now well acknowledged that functional β_1 and β_2-adrenoceptors coexist in the human heart. The human heart exhibits an almost uniform distribution of β-adrenoceptors between the left and right atrial and ventricular tissues. However, there is a minor difference in the β_1: β_2-adrenoceptor ratio between atrial and ventricular tissue, in the atria, it is approximately 60–70:40–30%, while in the ventricles, it is approximately 70–80:30–20% (Brodde OE *et al.*, 1999). The distribution of β_1 and β_2-adrenoceptors in the human heart can be influenced by pharmacological treatments or pathological conditions like heart failure. Consequently, a common characteristic of the failing human heart is a decrease in cardiac β-adrenoceptors, which is primarily (though not always) caused by a selective decrease in β_1-adrenoceptors, which causes the β_1: β_2-adrenoceptor ratio to shift in favor of β_2-adrenoceptors (Edward M *et al.*, 2000; Kaumann AJ *et al.*, 1997). The intracellular concentration of cyclic AMP is raised via the coupling of β_1 and β_2-adrenoceptors to adenylyl cyclase, which in turn causes an increase in contraction force and heart rate (Casteilla L *et al.*, 1994).

β_1-RECEPTORS

Adrenergic receptors, such as β_1, β_2, α_1, and α_2 receptors, are principally important for signalling in the sympathetic nervous system. Beta-agonists bind themselves to the beta receptors found in different human tissues. The kidney, fat cells, and the heart are the three organ systems that have the most β_1-receptors. G-protein coupled and communicates through the G_s alpha subunit is the β_1-adrenergic receptor. Adenylyl cyclase initiates a cAMP-dependent pathway upon receiving a signal from G_s, which enhances the receptor's action **(Figure 3)**. Heart rate and contractility are raised by targeted β_1 receptor activation, which also increases ventricular muscle firing, atrioventricular (AV) node, and sinoatrial (SA) node.

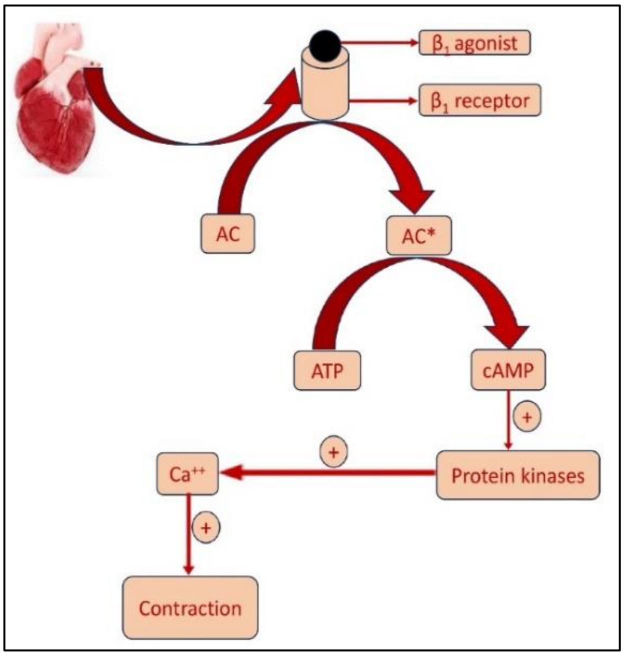

Figure 3: The beta-1 adrenergic receptor is a G-protein-coupled receptor communicating through the Gs alpha subunit. By signaling G_s, a cAMP-dependent pathway is initiated through adenylyl cyclase, and this results in the potentiation of the receptor's function

The cardiac output and stroke volume will both rise with higher values. The cardiac output equation makes this effect very evident. The product of heart rate and stroke volume is known as cardiac output. The targeted activation of the β_1-receptor will cause a rise in either stroke volume or heart rate. This will enhance cardiac output, which will increase tissue perfusion throughout the body (Aasakiran Madamanchi *et al.*, 2007). When the β_1-adrenoreceptor's G_s subunit is activated, it increases the activity of adenylyl cyclase, which converts ATP into cAMP. Calcium channels are phosphorylated by cAMP-dependent protein kinase A (PKA) in response to elevated cAMP levels, which raises intracellular calcium influx. Raising intracellular calcium concentrations causes the heart's inotropy to increase via the sarcoplasmic reticulum's calcium exchange process. Additionally, PKA phosphorylates myosin light chains, which cause smooth muscle cells to contract. One of the main components of the link between the sympathetic nervous system and the cardiovascular system is the β-AR signalling pathway (Abu Syed Md A *et al.*, 2008). Heart failure pathophysiology has been linked to deregulation of the β-AR pathway. Research has revealed that specific alterations to β-AR signalling leads to a 50% decrease in β_1-AR levels, while β_2-AR levels stay the same.

MUSCARINIC RECEPTORS

According to their location and receptor subtype, muscarinic receptors are spread out throughout the human body and mediate a variety of physiological processes (Dhein S *et al.*, 2001). Thus far, five distinct muscarinic receptor subtypes have been cloned and pharmacologically characterized; they are known as M_1, M_2, M_3, M_4, and M_5. The majority of researchers agree that the M_2 receptor is the most prevalent form of muscarinic receptor found in the human heart (Hulme EC *et al.*, 1990; Robert D Harvey *et al.*, 2003).

M_2-RECEPTOR

Pharmacologic evidence indicates the vast majority of functional responses in the heart are linked to M_2-receptor activation (Mery PF *et al.*,1997). Negative chronotropic and inotropic effects are produced by stimulation of these M_2-receptors. Stimulation of muscarinic receptors in human atria directly results in negative inotropic and chronotropic effects. In contrast, activation of receptors that coupled via Gs with adenylyl cyclase and increase cyclic AMP can only produce indirect negative inotropic effects in human ventricles. This means that effects cannot be demonstrated unless the basal force of contraction has been pre-heightened (Alrich L Gray *et al.*, 2004). The activation of M_2-receptors in the atria and ventricles, coupled with a PTX-sensitive G-protein (G_i / G_o), results in the inhibition of adenylyl cyclase, and this in turn hinders increases in intracellular cyclic AMP. This decreases the L-type Ca^{2+} current, which was previously enhanced by cyclic AMP, and seems to be the main mechanism of the indirect inhibitory action or inhibiting force of contraction enhanced by cyclic AMP elevating agents **(Figure 4)**. The parasympathetic nervous system provides the heart with a great deal of input when it is at rest. As a result, tonic muscarinic receptor activation lowers heart rate and suppresses the pacemaker cell’s intrinsic rate of firing (T Hussain *et al.*,1995). Additionally, AV conduction is slowed by the parasympathetic nervous system's tonic impact.

Muscarinic receptor antagonists, like atropine, can promote AV conduction and raise intrinsic heart rate. Conversely, the heart is less affected by resting sympathetic tone. Changes in the function of the SA and AV nodes are frequently reflected in the main effects of parasympathetic activation. However, the atria and ventricles also have a large amount of parasympathetic innervation, Muscarinic receptor agonists, and antagonist effects on cardiovascular function. All regions of the heart, including the ventricular myocardium, express muscarinic receptors. Muscarinic stimulation mostly leads to a reduction in the length of the action potential in atrial cells. Muscarinic receptor activation in ventricular tissue is not very effective unless it happens in conjunction with concurrent β-adrenergic receptor activation. The enhancement of contractility and stroke volume is the principal impact of β-adrenergic stimulation on ventricular function. Consequently, M_2-muscarinic receptor activation can significantly reduce cardiac contractility when β-adrenergic stimulation is present. Sympathetic and parasympathetic tones are thought to be altered reciprocally by autonomic responses that produce variations in cardiac output, such as those associated with baroreceptor reflexes (Relevic V *et al.*,1998). Another prevalent misperception is that inhibitory responses are invariably linked to muscarinic receptors in the cardiovascular system. In actuality, they are also connected to stimulatory effects. The most notable example is, which is the rebound stimulatory response that occurs when muscarinic receptor activation is discontinued. The fact that M_2 receptors concurrently activate stimulatory and inhibitory signalling pathways is reflected in this kind of stimulatory impact. When muscarinic receptors are activated, the inhibitory effect usually outweighs the stimulatory response. The two different responses and kinetics, however, differ significantly. The stimulatory response is considerably slower to turn on and off than the inhibitory impact, which is much quicker. Rebound increases in heart rate and contractility during brief variations in vagal stimulation are thought to be caused by this kind of rebound stimulatory response, which has been documented in both atrial and ventricular myocytes.

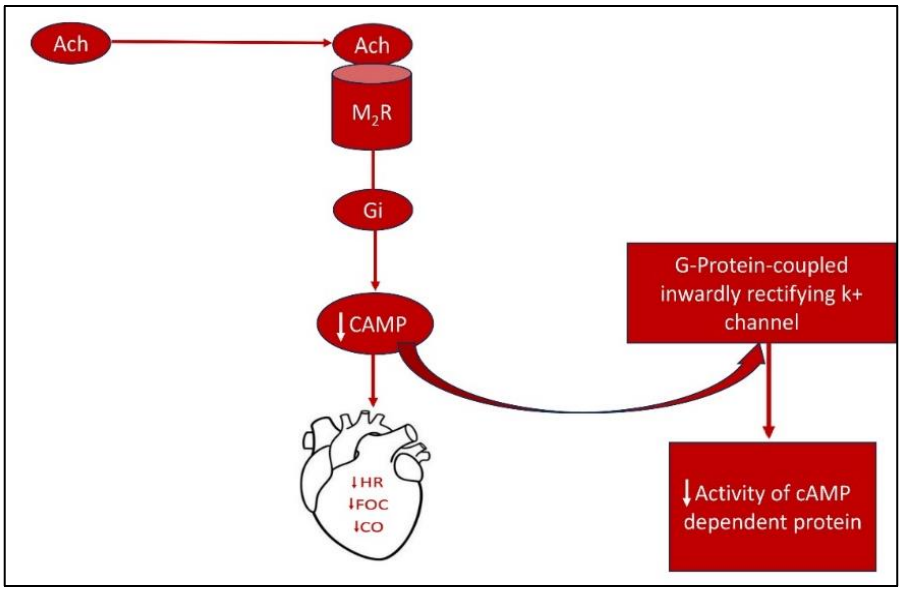

Figure 4: The M_2 muscarinic acetylcholine receptor (M2 receptor) is essential for the physiologic control of cardiovascular function through activation of G protein-coupled inwardly-rectifying potassium channels causes negative inotropic and chronotropic effects

ADENOSINE RECEPTOR

There are four recognized subtypes of adenosine receptors: A_1, A_{2A}, A_{2B}, and A_3 receptors (Headrick JP *et al*,2018). The heart has all four of the receptor subtypes, with different tissue distributions for each subtype. A_1R is highly expressed in the atria of the cardiovascular system and has a strong affinity for adenosine (Monahan TS *et al.*, 2000). A_1R expression is different in cardiac tissues: it is expressed at lower levels in ventricular myocytes than in the atrium and at higher levels in the right atrium compared to the left atrial. A_1R is also expressed in smooth muscles and endothelial coronary tissues. $A_{2A}R$ is widely expressed in the cardiovascular system but particularly in vessels, atria, and ventricular tissues. In ventricular myocytes, activation of $A_{2A}R$ leads to inotropic properties (JG Dobson Jr *et al.*, 1997; R Ray Morrison *et al.*, 2002). A R possesses the lowest affinity for adenosine. $A_{2B}R$ is expressed in myocytes and fibroblasts and is reported to modulate ventricular function in animals. $A_{2B}R$ is also expressed in smooth muscles of coronary arteries mediating vasodilation (Youn Kyoung Son *et al.*, 2005). A_3R myocardial expression is very low. Its expression, however, can be observed within the heart and appears to play a role in coronary artery muscle cells but also other smooth muscle cells (Zhao Z *et al.*, 2000; Bertil B *et al.*, 2011). If target cells release less cAMP as a result of A1R stimulation, voltage-gated calcium channels, and protein kinase A (PKA) is inhibited and phospholipase C is activated (Geoffrey Burnstock , 2017; Maryam Sharifi Sanjani *et al.*, 2011). The inwardly rectifying K+ current is also directly activated (cAMP-independent) upon activation of A1R. Voltage-gated Ca^{++} channels are likewise inhibited by $A_{2A}R$ activation. $A_{2A}R$ and, to a lesser extent, $A_{2B}R$ activation leads to vasodilation via NO and KATP channels, whereas A_1R activation causes bradycardia or atrioventricular block (AVB) (Dovenia S Ponnoth *et al.*, 2009). Moreover, $A_{2A}R$ blocks L Type calcium currents. There is some overlap in the cardiovascular consequences that follow A_1R or $A_{2A}R$ activation, even though they have different effects on cAMP synthesis in target cells. While all receptor subtypes seem involved in ischemic myocardium preservation, A_3Rs have been particularly linked to ischemia/reperfusion protection. Adenosine has a strong vasodilatory impact in the majority of arterial beds in mammals, as well as the ability to control coronary blood flow (CBF). These effects result from the activation of $A_{2A}R$ and A_2B receptors (Yoshikazu Kusano *et al.*, 2010). These effects also occur because smooth muscle cells produce factors that activate KATP channels and NO pathways in peripheral arterial vessels, as well as in coronary arteries(Zachary Berwick *et al.*, 2010).

CONCLUSION

The intricate functions of adrenergic receptors in the human heart are examined in this article, with muscarinic, adenosine, and α1, α2, and β-adrenoceptors receiving particular focus. The α_1-adrenoceptors, particularly the α_{1A} subtype, are crucial for positive inotropic effects and hypertrophic responses through the PLC/IP_3/DAG pathway. Higher levels of cyclic AMP are caused by β-adrenoceptors, specifically the β1 and β2 subtypes, resulting in increased cardiac output. Autonomic regulation is largely dependent on the negative inotropic and chronotropic activities of the M_2 subtype of muscarinic receptors. Bradycardia, ischemia/reperfusion protection, vasodilation, and other effects are some of the ways that adenosine receptors (A_1, A_{2A}, A_{2B}, and A_3) affect the heart. These receptor systems' complex interactions provide potential treatment approaches for cardiovascular disease. To properly understand the nuances of these signaling pathways and how they impact heart health, more research is required, with an emphasis on the intricate control mechanisms that govern cardiac function and pathology.

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