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Physiological and pathological roles of protein kinase a in the heart

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Abstract
Protein kinase A (PKA) is essential in controlling heart muscle function and structure. Its activation in cardiac cells is triggered by hormones, neurotransmitters, and stress-related catecholamines from the sympathetic nervous system. These catecholamines bind to β-adrenergic receptors, initiating a cAMP-dependent pathway that activates PKA. Elevated PKA activity enhances calcium ion cycling and cardiac muscle contractility, thereby improving heart performance.
Proper regulation of PKA is crucial for heart health. Disruptions in PKA signaling are linked to numerous heart conditions, including myocardial ischemia, hypertrophy, heart failure, and various cardiomyopathies such as diabetic, takotsubo, and anthracycline-induced types. PKA also plays a role in sex-related differences in heart function and disease susceptibility.
Recent studies emphasize the importance of understanding PKA's roles in both healthy and diseased hearts, identifying gaps in previous research and suggesting new avenues for investigation. Insights into the molecular mechanisms of PKA action offer potential for developing therapeutic interventions. Depending on the heart disease type and mechanism, targeting PKA with inhibitors or activators could be a viable cardio-protective strategy. Thus, creating specific PKA modulators as drugs holds promise for effectively treating various heart diseases.

Keywords: Norepinephrine, Isoproterenol, Adenylyl cyclase, Phosphodiesterase, AKAP

Introduction
Protein kinases have essential activities in almost all areas of cell biology and physiology, making their dysfunctions commonly linked to illnesses. The protein kinase A (PKA), also known as the 3', 5'-cyclic adenosine monophosphate (cAMP)-dependent protein kinase, was initially identified in 1968 and has since been considered the model for all protein kinases.PKA is a member of the AGC kinase family, which is called after its representative members PKA, 3′,5′-cyclic guanosine monophosphate (cGMP)-dependent protein kinase (PKG), and protein kinase C (PKC). The AGC kinase family consists of more than 60 serine/threonine protein kinases. PKA is evolutionarily conserved across many species, from fungus to humans, and is expressed in all kinds of mammalian cells. Two in the absence of cAMP, the PKA holoenzyme, which consists of two regulatory (R) and two catalytic (C) subunits, stays in an inactive form as a PKA tetramer (R2C2). The PKA regulatory (PKA-R) subunits consist of four isoforms: R1α, R1β, R2α, and R2β. These isoforms are encoded by the genes PRKAR1A, PRKAR1B, PRKAR2A, and PRKAR2B, respectively. On the other hand, the PKA catalytic (PKA-C) subunits have three known isoforms: Cα, Cβ, and Cγ. These isoforms are encoded by the genes PRKACA, PRKACB, and PRKACG, respectively. Three these isoforms vary in their patterns and degrees of expression and may demonstrate alternative splicing. The PKA holoenzyme is classified into type I and type II PKA, depending on the R subunit it contains. Type I PKA binds to R1, whereas type II PKA binds to R2. Typically, R1α and Cα1 are the most plentiful and widely distributed PKA-R and PKA-C subunits, respectively.
The canonical PKA signalling pathway is essential for the cardiac actions of many hormones and neurotransmitters, particularly the catecholamines including norepinephrine secreted by cardiac sympathetic nerve terminals, and epinephrine released by the adrenal medulla (Figure 1) [4]. Catecholamines bind the transmembrane β-adrenergic receptors (β-ARs),

major G-protein-coupled receptors in the heart, leading to release of the stimulatory G-protein α subunit ($G\alpha_s$) inside the target cells. $G\alpha_s$ then binds and activates adenylyl cyclases (ACs), which convert ATP is converted into cAMP, leading to a fast rise in intracellular cAMP levels. The cAMP molecules attach to the PKA-R subunits, causing the tetrameric PKA holoenzyme to separate. This separation results in the release of the individual PKA-C subunits, resulting to the activation of PKA. PKA phosphorylates many substrates to control cellular activity. It should be emphasized that in certain situations, the dissociation of the holoenzyme may not be required for the activation of PKA.5 PKA can be activated through non-canonical pathways that are not dependent on cAMP (Figure 1). This activation can be triggered by various stimuli, such as reactive oxygen species (ROS), lipopolysaccharides (LPS)/interleukin-1 (IL-1), endothelin-1 (ET-1)/angiotensin II (Ang II), transforming growth factor-β (TGF-β), sphingosine, and peroxynitrite. Thirteen For instance, R1α can function as a redox sensor and experience oxidant-induced protein degradation, resulting in the dissociation of PKA holoenzyme and the activation of the kinase.6 to 8 Furthermore, the PKA-C subunits are also confined by the inhibitor of κB (I-κB) proteins inside the I-κB-PKA-C complex, and can be stimulated upon I-κB breakdown [9, 10].

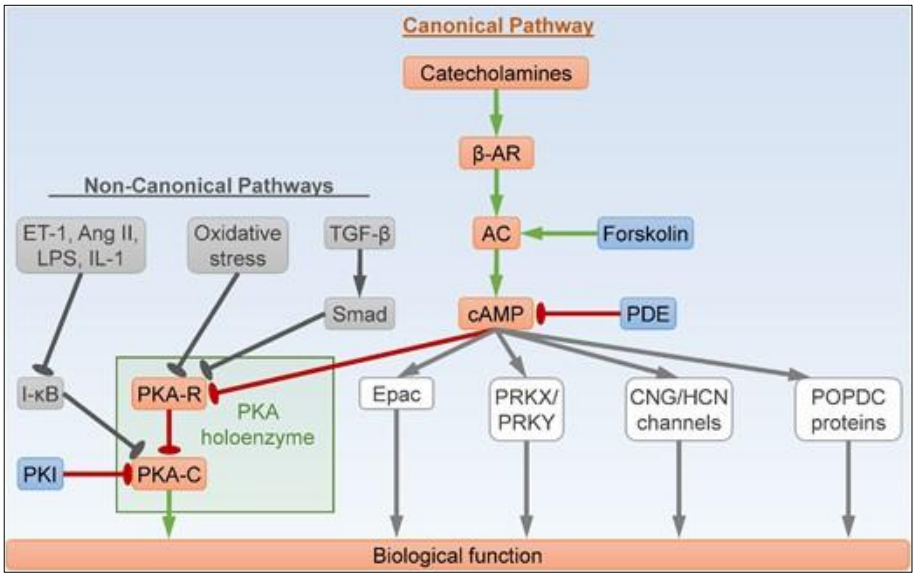

Fig 1: Biological function

The cellular levels of cAMP are regulated by the equilibrium between the enzymatic functions of ACs and cyclic nucleotide phosphodiesterases (PDEs). Unlike adenylate cyclases (ACs), phosphodiesterases (PDEs) break down cAMP into 5′-AMP, leading to a drop in cAMP levels and thus lowering PKA activity (Figure 1). Some phosphodiesterases (PDEs) have the ability to break down both cAMP and cGMP. Fourteen the function of PKA is hindered by the endogenous PKI protein, which acts as a pseudosubstrate of PKA. This protein is capable of capturing and deactivating the PKA-C subunits. Two Contrary to PKA-R, the relationship between PKI and PKA-C is not influenced by the concentrations of cAMP. A-kinase anchoring proteins (AKAPs) physically attach the PKA holoenzyme to various subcellular sites, enabling efficient and accurate regulation of its target molecules inside these distinct compartments. Fifteen For instance, the protein AKAP7, also referred to as AKAP15, attaches PKA to the plasma membrane in order to regulate the activity of L-type Ca2+ channels (LTCC, Cav1.2). On the other hand, muscle AKAP (mAKAP, AKAP6) and long AKAP7 (AKAP18) anchor PKA to the sarcoplasmic reticulum (SR) to control the functions of ryanodine receptors (RyRs) and sarco/endoplasmic reticulum Ca2+-ATPase (SERCA), respectively [15].

PKA has a crucial role in controlling and influencing the functioning, structure, and remodeling of the heart. Recent research has shown new functions of PKA in both healthy and sick hearts, shedding light on the underlying processes. In this article, we examine our current understanding of PKA's role in cardiac physiology and pathology.

2. PKA and cardiac contraction/relaxation

The contraction and relaxation of cardiac muscle control the systolic and diastolic activities of the heart. Contraction is triggered by electrical excitation, specifically the depolarization of the membrane caused by the action potential. This mechanism is known as excitation-contraction coupling. Sixteen the depolarization of the sarcolemma triggers the influx of calcium ions into the cell through the L-type calcium channels (LTCC). An increased concentration of Ca2+ in the cytosol stimulates the release of Ca2+ from the sarcoplasmic reticulum (SR) via the RyR2 channel, leading to a further elevation in the intracellular Ca2+ concentration. Calcium ions (Ca2+) attach to cardiac troponin C (cTnC), which alleviates the inhibitory effect of cardiac troponin I (cTnI) on the interaction between actin and myosin filaments, resulting in muscle contraction. During the relaxation of the heart, Ca2+ is separated from cTnC, moved back into the sarcoplasmic reticulum (SR) by SERCA, and expelled into the extracellular space through the Na+/Ca2+ exchanger (NCX) and the sarcolemmal Ca2+-ATPase.

PKA enhances contractile force via phosphorylating Cav1.2, PLN, and cMyBP-C. Phosphorylation of Cav1.2 or PLN enhances the amount of Ca2+ that is available, whereas phosphorylation of cMyBP-C enhances the capacity of the contractile apparatus to respond to Ca2+. Upon β-adrenergic

stimulation, protein kinase A (PKA) phosphorylates Cav1.2 at S1700, leading to heightened activity of the L-type calcium channel (LTCC) and an influx of calcium ions (Ca2+), ultimately intensifying muscle contraction. Eighteen findings conducted on knock-in mice expressing a non-phosphorylatable mutant of endogenous Cav1.2 (S1700A) confirm the hypothesis mentioned above. These findings demonstrate that the mutant animals exhibit lower basal and β-adrenergic-stimulated calcium currents, as well as reduced cardiomyocyte contractility. Eighteen Remarkably, the excessive production of the same Cav1.2 mutant (S1700A) using a transgenic method did not disrupt the flow of Ca2+, providing evidence that S1700 phosphorylation does not play a function. The number is 19. A recent research has found that PKA enhances the function of Cav1.2 channels by indirectly phosphorylating and depleting the inhibitor Rad. Twenty although there is an ongoing discussion on the specific processes involved, it is widely agreed that LTCC (L-type calcium channel) plays a crucial role in PKA-dependent calcium influx and cardiac contraction, as seen in Table 1. Phosphorylation of PLN by PKA at S16 removes the inhibitory effect of PLN on SERCA, leading to enhanced absorption of Ca2+ from the cytosol into the sarcoplasmic reticulum (SR) and subsequently increasing the amount of Ca2+ stored in the SR.25 Consequently, increased concentrations of Ca2+ can be discharged from the sarcoplasmic reticulum (SR) to attach to the contractile proteins, resulting in a more vigorous contraction. The physiological importance of RyR2 phosphorylation, which is dependent on PKA, has been a subject of debate. While there is evidence supporting the need of phosphorylation of RyR2 at S2808 by PKA for β-adrenergic-induced SR Ca2+ release and cardiac contraction, conflicting results have been documented. The numbers 30 and 31. The disparity may arise from the preference of either maximum or minimum RyR2 phosphorylation by PKA for promoting SR Ca2+ leak.32 Phosphorylation of cMyBP-C at S273, S282, or S302 by various kinases, including PKA, enhances the contractile strength of the heart by reducing the inhibitory effect of cMyBP-C on myosin, increasing the number of myosin heads involved in force production, or speeding up the cycling of cross-bridges, respectively. Therefore, the phosphorylation of cMyBP-C by PKA is a crucial regulator of cardiac inotropy.

3. PKA and ischaemic heart disease

Ischaemic heart disease, sometimes referred to as coronary artery disease, occurs when there is a decrease or obstruction in blood flow to the heart muscle, mostly caused by atherosclerosis. Previous literature has detailed the physiological roles of PKA in the development of atherosclerosis. 69 this study aims to provide a concise overview of our current understanding of PKA in myocardial ischemia, with a specific emphasis on cardiac myocytes. Myocardial ischaemia is defined as a condition when there is inadequate blood flow leading to tissue hypoxia, which is a state of oxygen deprivation. Reperfusion, which is the restoration of blood flow, leads to tissue re-oxygenation. However, it also paradoxically produces ischaemia/reperfusion (I/R) damage. During cardiac ischaemia, the content of catecholamines in the interstitial fluid increases significantly, by a factor of 100 to 1000 (Figure 2), 70, 71 as a result of the overstimulation of the sympathetic nervous system. The number is 72. Therefore, both the amount of cAMP and the activity of PKA are elevated in the myocardial affected by ischemia. After the restoration of blood flow, the amount of catecholamines in the heart decreases quickly and recovers to its original level within 120 minutes. The numbers 70 and 71. Nevertheless, the activity of PKA in the heart remains increased upon reperfusion, mostly due to the loss of R1α caused by oxidation and dimerization.8.77.

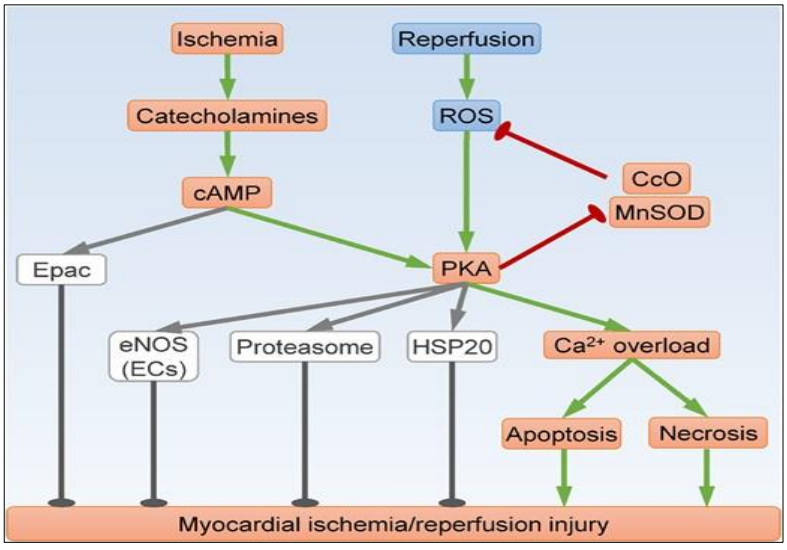

Fig 2: Myocardial ischemia/reperfusion injury

Catecholamines, at normal levels in the body, facilitate the fight-or-flight response by rapidly enhancing the force of muscle contractions and increasing the heart rate. At exceedingly high quantities, catecholamines can induce harm to the cardiac tissue. When rats are given a large amount of the man-made substance isoproterenol, it causes an increase in the phosphorylation of RyR2, which is dependent on the protein kinase A (PKA). This leads to the release of calcium ions from the sarcoplasmic reticulum (SR) and the death of heart muscle cells by either apoptosis or necrosis. This process is seen in Figure 2.33 In addition, isoproterenol stimulates the phosphorylation of cAMP-response element binding protein (CREB) at S133 through the activation of protein kinase A (PKA). This

phosphorylation enhances the binding of CREB to the cAMP-response element in the promoter region, resulting in the transcription of pro-apoptotic genes such as inducible cAMP early repressor (ICER) 46, 47 and Bim. Forty-eight it is important to mention that the lack of CREB does not affect apoptosis after I/R damage, most likely because CREB also controls the transcription of the anti-apoptotic gene Bcl-2 in specific situations. The number is 49. Moreover, the administration of isoproterenol in mice results in a temporary elevation in myocyte membrane permeability, which is a significant indicator of necrosis. The number is 78. Interestingly, it seems that acute catecholamine harm can be completely reversed. The value is 33.78. In contrast, continuous activation of the PKA substrate LTCC in mice leads to cardiac failure and early mortality, which is worsened by the infusion of isoproterenol. Isoproterenol exposure increases the activity of LTCC and improves the flow of Ca2+ into cells, resulting in an excessive amount of Ca2+ and the death of heart muscle cells.

The activation of β-AR/cAMP signaling during the ischemic phase is a contributing factor to myocardial I/R damage. Increased expression of PDE3A1 decreases the levels of cAMP in the heart muscle and weakens the apoptosis of myocytes generated by ischemia/reperfusion, maybe because of reduced ICER and enhanced Bcl-2 expression. The number is 79. Furthermore, administration of the β1-AR inhibitor CGP-20712A80 or the PKA inhibitor H89/PKI 42, 81 reduces the extent of myocardial necrosis caused by ischemia/reperfusion. Excessive levels of cAMP in the ischemic heart lead to the activation of PKA, which causes the phosphorylation and subsequent inhibition of cytochrome c oxidase (CcO). This inhibition results in an increase in the generation of reactive oxygen species (ROS).The number is 42. Consequently, oxidative stress induces the loss of R1α, which triggers the activation of PKA, 8, 77 resulting in further inhibition of CcO and formation of reactive oxygen species (ROS).7 Thus, a sudden increase in cAMP concentration might initiate a harmful cycle of oxidative stress by activating PKA (Figure 2).

The compounds forskolin, milrinone, olprinone, amrinone, trapidil, and dibutyryl-cAMP are all mentioned in the text.The numbers 75 and 84. Eliminating PDE3B from the reproductive cells enhances the amount of cAMP in the heart under normal conditions, decreases the magnitude of tissue damage caused by ischemia/reperfusion, and enhances cardiac performance. Eighty-seven Treatment with KT5720, a PKA inhibitor, prevents the cardioprotective effect of PDE3B ablation.87

4. PKA and cardiac hypertrophy

Chronic stimulation of β1-AR is widely recognized to cause cardiac hypertrophy. Four Nevertheless, it is still unclear if PKA plays a role in β1-AR-mediated hypertrophy. Prior research indicates that the targeted overexpression of β1-AR, Gαs, or PKA-Cα specifically in the heart significantly enlarges cardiomyocytes. However, this increase in cell size only has a small effect on overall heart weight, as it is accompanied by simultaneous apoptosis or necrosis. It is worth mentioning that β-adrenergic stimulation can induce apoptosis in adult cardiomyocytes, namely through a PKA-dependent mechanism [95]. Chronic infusion of isoproterenol leads to increased apoptosis and only a little increase in the size of cardiomyocytes when type 5 AC (AC5), a significant cardiac isoform, is overexpressed. The number is 96. AC5-mediated cAMP/PKA activation enhances oxidative stress by suppressing the expression of manganese superoxide dismutase (MnSOD) through a mechanistic process (Figure 2) [96]. The particular expression of AC6, a key cardiac isoform, in the heart does not affect the weight of the heart in mice with ischemic cardiomyopathy [97]. In addition, the excessive production of AC8 does not result in an increase in heart weight, even if PKA activity is four times higher [98]. These results indicate that the activation of PKA may predominantly induce the loss of myocytes, which might ultimately result in compensatory hypertrophy. Considering the crucial function of PKA in controlling cardiac contractility, it is logical to expect that interfering with PKA-dependent phosphorylation might disturb the normal functioning of the heart, perhaps leading to hypertrophic remodeling as a compensatory response to decreased cardiac output. Truly, animals with mutations in Cav1.2 that prevent phosphorylation [18, 24], PLN [99], cTnI [100], or cMyBP-C [37, 38] Cardiac impairment is observed in individuals with PKA site mutations. Undoubtedly, the activation of nuclear PKA is linked to an increase in ventricular hypertrophy, as seen in Figure 3. When nuclear-targeted PKA-C is overexpressed, it leads to an increase in the size of cardiomyocytes. On the other hand, overexpression of cytosolic-targeted PKA-C boosts Ca2+ transients and cardiac contractile power without causing hypertrophy. One hundred and ten β-Adrenergic stimulation or pressure overload-induced hypertrophy necessitates the presence of sAC, which is responsible for facilitating nuclear cAMP production.111 Notably, the activation of β1-AR leads to an increase in nuclear PKA activity, which in turn causes hypertrophy. 93 In contrast, the activation of β2-AR does not lead to nuclear PKA activation, 47 and does not result in hypertrophy [112]. Mechanistically, PKA phosphorylates CREB at serine 133 inside the nuclei of cardiomyocytes, therefore beginning the transcription of hypertrophy-related genes through CREB-mediated mechanisms. The numbers 49 and 50. Cardiac-specific PKI transgenic animals, which have β1-AR-mediated nuclear PKA activation blocked by PKI,47, exhibit resistance to isoproterenol-induced CREB phosphorylation at S13327 and consequent pathological hypertrophy.89 In addition, the overexpression of a mutant form of CREB (S133A) that cannot be phosphorylated reduces the development of hypertrophy generated by isoproterenol [46]. These data indicate that CREB-mediated transcription plays a crucial role in promoting hypertrophy and is controlled by nuclear PKA. The activation of nuclear PKA by β-AR signaling necessitates the presence of the scaffold protein mAKAP. The number is 47. Remarkably, mAKAP assists in the calcineurin-dependent activation of the pro-hypertrophic transcription factor nuclear factor of activated T cells (NFAT). NFAT binds to GATA4 or myocyte enhancer factor 2 (MEF2) to promote the expression of genes relevant to hypertrophy. Glycogen synthase kinase-3β (GSK-3β) is responsible for phosphorylating NFAT, leading to its nuclear export and inactivation. This process is inhibited by PKA through PKA-dependent phosphorylation at S9 [53]. Thus, nuclear PKA can enhance hypertrophy in collaboration with calcineurin by counteracting the inhibitory effect of GSK-3β on NFAT (As shown in Figure 3). Consistent with our results, global PKA-Cβ null animals exhibit resistance to

Ang II-induced cardiac hypertrophy. One hundred fourteen Interestingly, an excessive amount of PKA-Cα in cardiac fibroblasts also causes the enlargement of the ventricles and the growth of cardiomyocytes, maybe through a paracrine mechanism. One hundred and fifteen PKA plays a role in promoting ventricular hypertrophy whether it is present in the nuclei of cardiomyocytes or in cardiac fibroblasts.

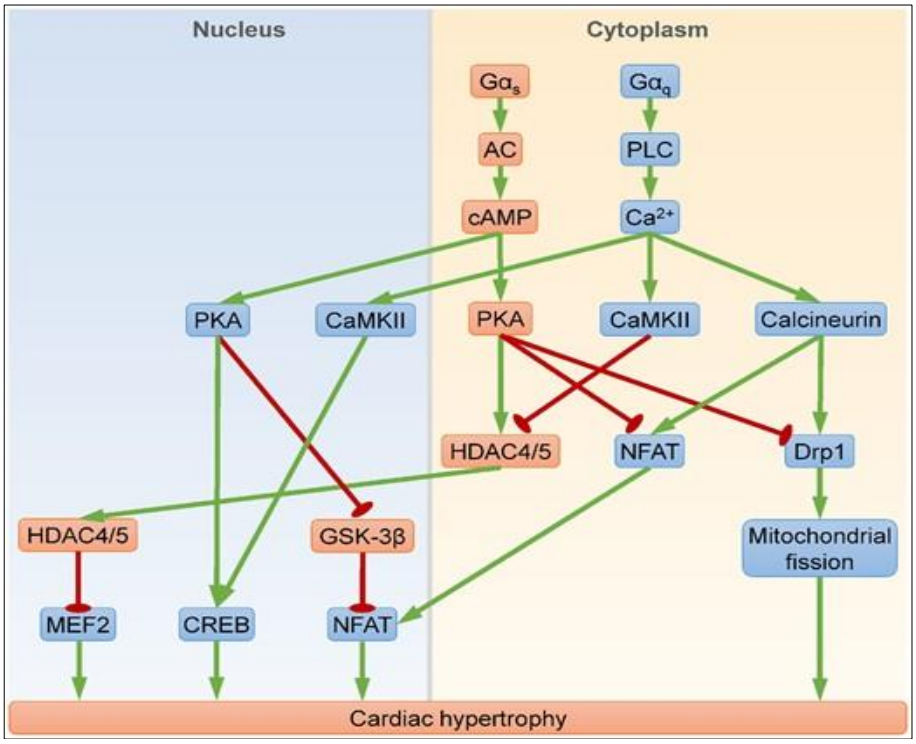

Fig 3: Cardiac hypertrophy

On the other hand, there is increasing evidence indicating that cytoplasmic PKA could impede hypertrophy. When PDE2 is inhibited, it causes a rise in the amount of cAMP in a specific area. This increase in cAMP leads to the phosphorylation of NFAT at certain sites (S245/S269/S294) by PKA. As a result, NFAT is kept in the cytoplasm and hypertrophy is inhibited. 54 The retention of NFAT in the cytoplasm is dependent on the localization of PKA in the mitochondria. When AKAP1 (Also known as AKAP121), which directs PKA to the mitochondria, is disrupted, the activity of PKA in the mitochondria decreases. This results in increased accumulation of NFAT in the nucleus and worsened hypertrophy, both in laboratory settings and in living organisms. The numbers are 55 and 56. These findings indicate that cytoplasmic PKA has the ability to directly suppress NFAT, as seen in Figure 3. Recently, we deleted the gene PRKAR1A, which encodes R1α, in the mouse heart to investigate the effects of cytoplasmic PKA activation on physiological cardiac hypertrophy throughout development. This is because R1α restricts cytoplasmic PKA activity. 57 Due to the fact that completely removing both copies of the PRKAR1A gene prevents heart muscle cells from dividing and leads to death before birth, we instead partially remove one copy of the gene. Our study demonstrates that this partial removal of PRKAR1A hinders the growth of the heart muscle in a way that is likely caused by the inhibition of mitochondrial fission through the phosphorylation of Drp1 at S637 by PKA (as shown in Figure 3). Significantly, mutations/deletions in the PRKAR1A gene in humans are also linked to a decrease in the size of the left ventricle of the heart.57 Furthermore, the elimination of germline PRKAR2B weakens the development of age-related cardiac hypertrophy, maybe through a mechanism that is not dependent on cardiomyocytes, as R2β is mostly expressed in non-cardiac organs [118].

While the activation of Gαs-coupled receptors such as β1-AR, or Gαq-coupled receptors such as α1-AR, Ang II type 1 receptor, and ET A receptor, may both cause cardiomyocyte hypertrophy, it seems that Gαs signaling counteracts Gαq-mediated hypertrophy. For instance, the administration of forskolin (A compound that activates adenylate cyclase) 57, or cAMP58, reduces the hypertrophy induced by α1-AR in laboratory experiments. In addition, the activation of Gαq, which is responsible for the expression of genes associated with cardiac hypertrophy, is inhibited by isoproterenol, forskolin, or a specific PKA activator called 8-CPT-6-Phe-cAMP. Conversely, the expression of these genes is increased by a PKA inhibitor known as H89.One hundred nineteen From a mechanistic standpoint, the activation of protein kinase A (PKA) that is dependent on Gαs leads to the phosphorylation of histone deacetylase 5 (HDAC5) at S279 58,59 or the dephosphorylation at S259/S498,120. This, in turn, causes the movement of HDAC5 from the cytoplasm to the nucleus. Once in the nucleus, HDAC5 suppresses the transcription of the hypertrophic gene program that is mediated by MEF2 (Figure 3). PKA also triggers the transportation of HDAC4 into the nucleus, leading to the suppression of MEF2.The number is 60. In contrast, Gαq activates phospholipase C, which in turn raises the amount of intracellular Ca2+. This leads to the activation of Ca2+/calmodulin-dependent protein kinase type II (CaMKII) and calcineurin (also known as protein phosphatase 2B). Interestingly, CaMKII stimulates the export of HDAC4 from the nucleus to trigger MEF2-mediated severe cardiac hypertrophy.121 However,

calcineurin removes phosphate groups from NFAT at S245/S269/S294 and Drp1 at S637, which are the identical locations where cytoplasmic PKA adds phosphate groups [122, 123]. Therefore, cytoplasmic PKA may counteract CaMKII- and calcineurin-mediated hypertrophy (Figure 3). It is worth noting that CaMKII also phosphorylates CREB at S133 [124], suggesting that CaMKII and nuclear PKA may promote CREB-dependent hypertrophy in a redundant manner.

5. PKA and heart failure

Human heart failure is linked to reduced phosphorylation of PLN,125 cTnI,126–128 and cMyBP-C.128,129 While the exact explanation of the disparity is still a subject of ongoing dispute, 130 animal models of heart failure demonstrate an elevated level of cTnI phosphorylation. The number is 131,132. In rabbit cardiomyocytes that are not functioning properly, the activation of PKA by β-AR is reduced at the sarcoplasmic reticulum (SR) and sarcolemma, but increased at the myofilaments. This suggests a redistribution of intracellular PKA activity [132]. As a result, the phosphorylation of the SR protein PLN by PKA is reduced, whereas the phosphorylation of the myofilament protein cTnI is enhanced in failed myocytes. The activation of PKA in heart failure is caused by a decrease in local PDE activity and an increase in β2-AR signaling. Heart failure is mechanistically linked to a shift of β2-AR and PKA from t-tubules to other parts of the sarcolemma due to decreased production of caveolin-3, a key structural protein of caveolae [132-134]. It is important to mention that the overall PKA activity after cAMP stimulation is similar in both failing and non-failing human hearts. This suggests that heart failure exclusively affects PKA signaling at the level of β-AR. However, human hearts that are not functioning properly exhibit reduced levels of R1α [126, 136], but opposite findings have also been reported [128].

The heart's proper operation depends on the effective cycling of Ca2+, which is regulated by the phosphorylation of the Ca2+ handling proteins by PKA in a very dynamic way. Thus, the extended activation or inhibition of PKA and its substrates might lead to the development of heart failure. For instance, one can either acquire- [99, 137] Loss-of-function PLN mutations, namely those with a deleterious effect, result in the development of fatal dilated cardiomyopathy. Continuous activation of long-term calcium channel (LTCC) triggers excessive calcium (Ca2+) accumulation in cardiomyocytes, resulting in cell death (necrosis) and ultimately leading to heart failure [23]. Conversely, when LTCC is permanently deactivated, it leads to cardiac failure and untimely mortality [24]. Continuous activation of PKA results in excessive phosphorylation of PLN and RyR2, which causes a decrease in contractile function, enlargement of the heart muscle, and abrupt cardiac death. The number is 28. While continuous suppression of PKA in mice does not result in any functional or structural problems, reduced PKA activity hinders the heart's ability to adjust to stress and may contribute to the development of heart failure [27].

Heart failure selectively influences the expression of the PDE family members. Human heart failure is linked to reduced levels of PDE3A and PDE4D, which are enough to cause SR Ca2+ leakage and the death of heart muscle cells [68, 107]. Interestingly, failing human hearts express higher levels of PDE1C [105], PDE2 [139], and PDE10A [106], These enzymes break down cAMP and may lead to a reduced contractile response. Blocking PDE1C enhances the production of cAMP through the adenosine A2 receptor (A2R), resulting in immediate improvements in cardiac contractility, relaxation, and blood vessel dilation in heart failure produced by rapid pacing [140]. Similarly, inhibition of PDE2 [141] or PDE10A [106] protects against pressure overload-induced heart failure. Since inhibition of PDE1C [105], PDE2 [141], or PDE10A [106] Furthermore, the elevation of cardiac cGMP levels is also associated with the cardio-protective effects, which are believed to be influenced by both cAMP-dependent and cAMP-independent pathways.

6. PKA and cardiomyopathies

6.1 Diabetic cardiomyopathy

Recent findings indicate that catecholamines inhibit the transport of glucose in the heart that is caused by insulin. The number is 144. Prolonged activation of catecholamines not only contributes to the advancement of heart failure, but also results in insulin resistance inside the heart. One hundred forty-five from a mechanistic standpoint, excessive activation of β2-AR in cardiomyocytes hinders the movement of glucose transporter 4 (GLUT4) to the plasma membrane, which is normally stimulated by insulin. This leads to a decrease in glucose uptake, and the process is dependent on PKA. One hundred forty-five Administration of the β-blockers propranolol or metoprolol effectively inhibits the development of myocardial insulin resistance generated by catecholamines [145]. Catecholamines stimulate lipolysis in adipocytes through a PKA-dependent mechanism. This inhibits the translocation of GLUT4, a protein involved in glucose uptake, which is normally triggered by insulin signaling through the phosphoinositide 3-kinase/Akt/mammalian target of rapamycin pathway. As a result, there is a reduction in glucose absorption [146].

Insulin resistance, a prevalent characteristic of type 2 diabetes mellitus, can lead to heart dysfunction by causing a decrease in total PKA activity through PDE4D.147 In individuals with type 2 diabetes, an excessive amount of insulin leads to the production of PDE4D through the activation of the β2-AR/β-arrestin2/extracellular signal-regulated kinase pathway, which is dependent on G-protein-coupled receptor kinase 2 (GRK2).147 Thus, administering the GRK2 inhibitor paroxetine or the β-blocker carvedilol reduces PDE4D expression, restores cAMP/PKA activity, and protects against cardiac dysfunction associated with type 2 diabetes [147]. Notably, type 1 diabetes is linked to lower myocardial contractility as a result of diminished PKA activity [148]. Given that type 1 diabetes is defined by a lack of insulin, it may be required to have a normal amount of insulin in order to activate cardiac PKA. Collectively, these results indicate that an overabundance or insufficiency of insulin can reduce the activity of PKA in the heart muscle and lead to diabetic cardiomyopathy.

6.2 Takotsubo cardiomyopathy

Takotsubo cardiomyopathy, often referred to as stress cardiomyopathy, shattered heart syndrome, or apical ballooning syndrome, is a kind of sudden and temporary heart failure that usually arises following physical or mental stress. The occurrence of takotsubo cardiomyopathy is significantly higher during the coronavirus illness 2019 pandemic, either as a result of coronavirus infection or the psychological stress associated with the pandemic.[150] Takotsubo cardiomyopathy can result in persistent structural

and metabolic alterations, as well as a heart failure phenotype, despite the typical recovery of heart function within a few weeks [151]. Takotsubo cardiomyopathy is linked to increased levels of catecholamines in the bloodstream and heart muscle, which can exceed those observed after an acute myocardial infarction [152]. High levels of catecholamines directly cause cardiac contraction band necrosis, which is a characteristic pathological feature of takotsubo cardiomyopathy [152]. Furthermore, catecholamines cause significant lipid buildup in the heart, leading to the development of lipotoxicity. One hundred and fifty-three Genetic defects can lead to an increased vulnerability to takotsubo cardiomyopathy due to catecholamine hypersensitivity. This is driven by the excessive phosphorylation of RyR2, PLN, cTnI, and Cav1.2, which is mediated by PKA [154]. Thus, it is plausible that there is a hereditary inclination towards developing takotsubo cardiomyopathy, but this has to be studied and defined more extensively.

7. PKA and the sex differences in cardiac health or disease

Biological sex has a substantial impact on the heart. Pre-menopausal women have higher baseline cardiac function and demonstrate a lower vulnerability to cardiovascular disease compared to males of the same age. Female individuals with superior cardiac function have heightened baseline PKA activity and demonstrate differential gene expression patterns in their cardiomyocytes, indicating a fundamental differentiation between female and male cardiomyocytes [159]. Moreover, the existence of the female sex hormone oestrogen has the ability to activate the cAMP/PKA pathway and enhance the force of cardiac contractions under normal conditions. The numerical values 160 and 161 Female hearts and myocytes exhibit diminished contractions compared to males in response to stimuli such as exercise, stress, and disease, as a result of increased demand. One possible explanation is that oestrogen opposes the effects of catecholamines, resulting in a reduction of intracellular cAMP levels and inhibition of the release of SR Ca2+.The integers [163] and [164]. Based on the above facts, our hypothesis is that estrogen counteracts the fight-or-flight response, which is controlled by catecholamines, by elevating cAMP levels in many cellular compartments. However, this possibility needs be confirmed by other research.

8. Conclusions and perspectives

Preclinical research conducted in the past several decades have significantly enhanced our comprehension of PKA in cardiac physiology. PKA controls cardiac muscle contraction, relaxation, and heart rate via influencing the movement of Ca2+ in cardiac myocytes. The activation of myocardial PKA can occur through both the canonical and non-canonical routes. The classical PKA route involves the activation of cAMP-dependent PKA through the stimulation of β-AR by catecholamines. The non-canonical pathways stimulate PKA activity in a manner that is not dependent on cAMP. Anomalous PKA activity has been detected in many heart diseases. Hence, PKA possesses the capacity to function as a pharmaceutical target for the management of cardiovascular disorders.

Although significant advancements have been made in recent years, there is still a lack of complete understanding of the specific functions of PKA in the development of cardiac disease. Areas of investigation that are crucial and require further examination include:

- The regulation of PKA activity in relation to time and space in both healthy and diseased hearts.
- The proteins responsible for determining the localization of PKA within cells.
- The influence of PKA on the shape, destiny, and function of heart muscle cells.
- The signaling pathways that control cell death (apoptosis/necrosis) downstream of PKA.
- The connections between PKA and oxidative stress in the heart.
- Identifying additional proteins that PKA interacts with in the heart.
- Understanding the role of PKA in the differences between sexes in terms of heart disease.
- Determining which types of heart disease would benefit from interventions that either activate or inhibit PKA.
- Investigating the negative effects that can arise from activating or inhibiting PKA.
- Developing potent and specific compounds that can activate or inhibit PKA.

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