Proceedings of the 2nd International Conference on Modern Medicine and Global Health
DOI: 10.54254/2753-8818/33/20240895

The role of protein kinase A signaling in cardiomyopathy

Acacia Yuan

Logan High School, Logan, UT 84321, USA

acaciafengyuan@gmail.com

Abstract. Cardiomyopathy, a diverse group of heart muscle diseases, poses a significant challenge to global cardiovascular health. However, the intricate molecular mechanisms underlying cardiomyopathy, especially the pivotal role of protein kinase A (PKA) signaling pathways in its pathogenesis, remains unclear. The review synthesizes current research findings and highlights the multifaceted interactions between PKA and key cellular components implicated in cardiomyopathy progression. Moreover, this paper unfolds with an exploration of the normal physiological functions of PKA in cardiac cells, emphasizing its role in regulating crucial processes such as excitation-contraction coupling and cellular energy homeostasis. The article navigates through the dysregulation of PKA signaling observed in various forms of cardiomyopathy, including hypertrophic, dilated, and restrictive subtypes. Insightful analyses into the impact of PKA-mediated phosphorylation events on cardiac contractility, ion channel function, and mitochondrial dynamics shed light on the intricate interplay between signaling cascades and disease manifestation. Future clinical trials targeting the PKA signaling pathway are required to seek more effective and precise therapeutic approaches of cardiomyopathy.

Keywords: protein kinase A, cardiomyopathy, physiological function

1. Introduction

Cardiomyopathy refers to a group of diseases that affect the heart muscle, leading to structural and functional abnormalities. In these conditions, the heart muscle becomes weakened, making it harder for the heart to pump blood and deliver it to the rest of the body. As a result, the body may not receive an adequate supply of oxygen and nutrients [1]. The causes of cardiomyopathy can vary and may include genetic factors, infections, autoimmune diseases, and certain medications. In some cases, the cause is unknown. It's essential for individuals with symptoms of cardiomyopathy to seek prompt medical attention. Early diagnosis and management can help improve the quality of life and outcomes for those affected by this condition [2].

The protein kinase A (PKA) signaling pathway is a crucial intracellular signaling mechanism that plays a central role in regulating various cellular processes. PKA is a serine/threonine kinase that is activated in response to elevated levels of cyclic adenosine monophosphate (cAMP), a second messenger. PKA signaling pathway is involved in the transduction of extracellular signals to intracellular responses, making it essential for cellular function and homeostasis [3]. Dysregulation of the PKA signaling pathway has been implicated in various diseases, including cancer, cardiovascular diseases, and neurological disorders. Aberrant PKA activity can contribute to uncontrolled cell proliferation, altered

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cardiac contractility, and impaired synaptic function. Previous research suggested the relationship between the PKA signaling pathway and cardiomyopathy [4, 5].

This review summarizes the role of the PKA signaling pathway in cardiomyopathy, to better elucidate potential mechanisms of cardiomyopathy and provide insights into therapeutic targets.

2. Physiological role of PKA signaling pathway

2.1. Overview of PKA signaling pathway

PKA is a serine/threonine kinase that exists in an inactive form as a tetramer consisting of two regulatory (R) subunits and two catalytic (C) subunits. In its inactive state, the R subunits inhibit the activity of the C subunits. Activation of PKA is initiated by the binding of cAMP to the regulatory subunits, inducing a conformational change that releases the catalytic subunits. Liberated catalytic subunits are then free to phosphorylate target proteins, initiating a downstream signaling cascade [6].

The production of cAMP, a key activator of PKA, is tightly regulated by the activity of adenylate cyclase. Adenylate cyclase is activated by G protein-coupled receptors (GPCRs) in response to various extracellular signals, such as hormones or neurotransmitters. This activation leads to the conversion of ATP into cAMP, amplifying the signal and activating PKA (figure 1) [7].

PKA is compartmentalized within the cell, ensuring specificity in its actions. A-kinase anchoring proteins (AKAPs) facilitate the spatial and temporal regulation of PKA by tethering the enzyme to specific subcellular locations. The target proteins of PKA are diverse and include transcription factors, ion channels, and other kinases, allowing for the modulation of a wide array of cellular functions [8].

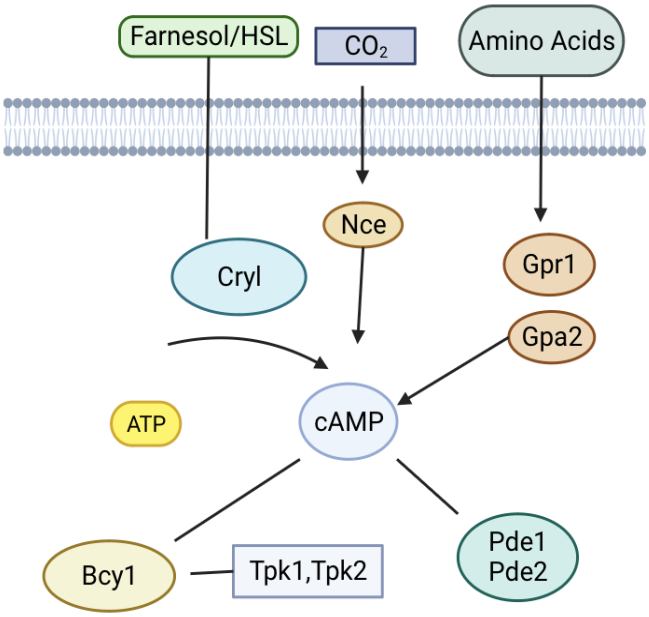

Figure 1. Process of the PKA signaling pathway. CO_2, amino acids, as well as HSL, are key factors and reactants that come from outside the phospholipid wall needed in the process. ATP, Bcy1, and Pde 1 and 2 are involved in signal transduction within the cell. PKA, protein kinase A; cAMP, cyclic adenosine monophosphate; HSL, hormone-sensitive lipase; Nce, a new chemical entity; Bcyl, the regulatory subunit of PKA; Tpk, Thiamin Pyrophosphokinase; Pde1, calmodulin-dependent cyclic nucleotide phosphodiesterase; Pde2, phosphodiesterase 2; Gpr1, G protein-coupled receptor 1; Gpa2, a G-protein α subunit. Figure credit: original. Figure created in Biorender.com.

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2.2. Physiological Functions of PKA

The PKA signaling pathway is involved in the regulation of numerous physiological processes (table 1). In metabolism, PKA influences glycogen breakdown and lipid metabolism. In gene expression, PKA regulates the activity of transcription factors such as CREB (cAMP response element-binding protein). Additionally, PKA plays a critical role in cell cycle progression, cell growth, and synaptic plasticity [6].

Metabolism regulation involves various processes that are influenced by the activation of PKA. In the breakdown of glycogen into glucose, PKA plays a regulatory role, responding to hormonal signals and affecting energy availability. Additionally, PKA activation impacts lipid metabolism, influencing processes such as lipolysis (the breakdown of fats) and adipocyte function [9].

In terms of gene expression and regulation, PKA is actively involved in transcriptional regulation. This includes the phosphorylation of transcription factors, such as CREB (cAMP response element-binding protein), which modulates gene expression in response to cAMP signaling. Furthermore, PKA mediates cellular responses to hormones and neurotransmitters by influencing the expression of specific genes [10].

Regarding cell cycle progression and proliferation, PKA contributes to cell division and cell cycle progression by influencing the activity of proteins involved in these processes. Dysregulation of PKA signaling can lead to uncontrolled cell proliferation, which is a characteristic feature of conditions like cancer [11]. In cellular differentiation, PKA can influence cell fate determination by regulating the activity of transcription factors involved in these processes. This highlights the diverse and critical roles that PKA plays in various cellular and physiological functions [11].

In the realm of neuronal signaling and synaptic plasticity, PKA regulates synaptic transmission in neurons by modulating the function of ion channels and neurotransmitter release. Moreover, PKA is crucial for synaptic plasticity, playing a role in the molecular mechanisms that underlie learning and memory [12]. Ion channel regulation is another area where PKA exerts its influence. By phosphorylating ion channels, PKA affects their activity and influences ion transport across cell membranes. In neurons, PKA also regulates ion channels, contributing to the control of neuronal excitability [13].

In terms of cardiac function, PKA is involved in regulating the contractility of cardiac muscle cells and influencing heart rate. This is achieved by phosphorylating proteins involved in the excitation-contraction coupling process and modulating ion channels, particularly in the sinoatrial node [5].

PKA is a key player in the Cellular Response to Stress, particularly in the “fight-or-flight” response triggered by adrenaline. It is integral to the physiological reactions that occur in response to stress. In terms of Immune Function, PKA signaling is involved in the modulation of immune responses. PKA signaling pathway influences processes such as cytokine production and immune cell activation, contributing to the regulation of the immune system [14].

Table 1. Physiological role of PKA signaling pathway.

Process	Effects	References
Metabolism regulation	Breakdown of glycogen, lipolysis, adipocyte function	[9]
Gene expression	Phosphorylation of transcription factors	[10]
Cell cycle	Cell division and proliferation	[11]
Cell differentiation	Cell fate determination related transcription factors	[11]
Neuronal signaling	Ion channels and neurotransmitter release.	[12]
Cardiac function	Phosphorylation of excitation-contraction coupling proteins	[5]
Immune system	Cytokine production and immune cell activation	[14]

Understanding the diverse functions of the PKA signaling pathway is crucial for appreciating its role in maintaining cellular homeostasis and responding to external stimuli, and it provides valuable insights into the mechanisms underlying various physiological and pathological conditions [15].

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2.3. PKA Signaling and Cardiac Contraction/Relaxation

The PKA signaling pathway is a fundamental intracellular cascade that plays a crucial role in cellular regulation, influencing various physiological processes. One of its key areas of impact is in the context of cardiac contraction and relaxation, making it a critical player in cardiovascular health. This brief overview explores the significance of PKA signaling, particularly its involvement in modulating cardiac function.

The heart's ability to contract and relax rhythmically is essential for maintaining effective blood circulation throughout the body. PKA signaling is intricately linked to this dynamic process and exerts a profound influence on cardiac function [16].

Regulation of cardiac function by PKA activation encompasses several key mechanisms. Firstly, in terms of Contractility Regulation, PKA activation plays a crucial role in influencing cardiac contractility. This is achieved through the phosphorylation of essential proteins involved in the excitation-contraction coupling process. Notably, troponin I, a regulatory protein in the sarcomere, undergoes phosphorylation, resulting in increased myofilament sensitivity to calcium ions and a subsequent enhancement of the force of contraction [17].

Furthermore, PKA signaling has a significant impact on Calcium Handling within cardiac muscle cells. Phosphorylation events, orchestrated by PKA, target key proteins involved in calcium regulation. This includes the phosphorylation of L-type calcium channels and phospholamban, which collectively enhance calcium influx during contraction and facilitate the reuptake of calcium into the sarcoplasmic reticulum during relaxation [5].

The sympathetic nervous system's role in cardiac function is highlighted through Beta-Adrenergic Stimulation. Activation of the PKA signaling pathway in cardiac cells, triggered by the release of adrenaline, leads to a cascade of effects. This process, known as beta-adrenergic stimulation, results in increased heart rate, heightened contractility, and improved relaxation. These dynamic adjustments allow the heart to respond effectively to changing physiological demands [18].

In addition to its acute effects, PKA activation confers Cardioprotective Effects by promoting the phosphorylation of proteins involved in stress adaptation. This includes the modulation of potassium channels and activation of anti-apoptotic pathways. The culmination of these processes contributes to the heart's resilience under conditions of stress, showcasing PKA's role in maintaining cardiac health and function [19].

Understanding the intricate interplay between PKA signaling and cardiac contraction/relaxation is pivotal for unravelling the mechanisms underlying normal cardiac function and the pathophysiology of cardiovascular diseases. Dysregulation of PKA signaling in the heart is associated with conditions such as heart failure, arrhythmias, and cardiomyopathies, emphasizing the therapeutic potential of targeting this pathway for cardiovascular interventions. In summary, the PKA signaling pathway emerges as a central player in maintaining the delicate balance of cardiac dynamics, making it a focus of intense research and a potential avenue for innovative cardiovascular therapies [20].

3. Targeting PKA signaling pathway in cardiomyopathy

3.1. PKA Signaling pathway in disease.

PKA signaling is vital for the regulation of diverse cellular functions, including metabolism, gene expression, cell growth, and differentiation. It acts as a key mediator in response to hormonal signals, such as those from adrenaline or glucagon, and helps coordinate the cellular response to changing environmental conditions [5].

The dysregulation of the PKA signaling pathway has been implicated in various diseases, highlighting its importance in maintaining cellular balance. Notably, abnormalities in PKA signaling have been associated with several cardiac conditions, including cardiomyopathies, arrhythmias, and heart failure [5]. In the context of heart diseases, the PKA signaling pathway is particularly significant. It regulates the contractility of cardiac muscle cells, influencing the pumping function of the heart.

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Dysfunctional PKA signaling can lead to impaired cardiac function, contributing to the development and progression of heart-related disorders [12].

Beyond cardiac implications, aberrant PKA signaling has been linked to a range of diseases, including cancer, neurodegenerative disorders, and endocrine disorders. Understanding the intricacies of this signaling pathway provides insights into potential therapeutic targets for these conditions.

In conclusion, the PKA signaling pathway serves as a central player in cellular signaling, influencing a multitude of physiological processes. Its dysregulation is associated with various diseases, with particular relevance to cardiac conditions. Investigating the molecular mechanisms underlying PKA signaling in health and disease is crucial for developing targeted therapeutic strategies and advancing our understanding of cellular signaling networks [4].

3.2. Effects of aberrant PKA Signaling pathway in cardiomyopathy.

The PKA signaling pathway undergoes significant alterations in the context of cardiomyopathies, contributing to the pathogenesis and progression of these cardiac disorders. Cardiomyopathies are characterized by structural and functional abnormalities in the heart muscle, and dysregulation of PKA signaling is implicated in several key aspects of these conditions [5].

In the context of altered β-adrenergic signaling, normal cardiac function involves sympathetic stimulation activating beta-adrenergic receptors, leading to the activation of PKA. This activation enhances cardiac contractility and relaxation. However, certain cardiomyopathies exhibit dysregulation in beta-adrenergic signaling. This dysregulation may manifest as desensitization of beta-adrenergic receptors, reduced cAMP production, or impaired coupling between receptors and adenylate cyclase, ultimately compromising the activation of PKA [21].

Aberrant calcium handling is another aspect affected in cardiomyopathies. While PKA normally modulates the activity of calcium-handling proteins, such as the ryanodine receptor and phospholamban, disruptions in these proteins can occur in cardiomyopathies. These alterations disturb the delicate balance of intracellular calcium levels, leading to impaired contractility and relaxation during the cardiac cycle [22].

Changes in Troponin I Phosphorylation further contribute to altered contractile dynamics in cardiomyopathies. Troponin I, a key regulatory protein in the sarcomere, undergoes PKA phosphorylation, enhancing myofilament sensitivity to calcium. However, aberrant troponin I phosphorylation in cardiomyopathies can result in altered contractile dynamics, leading to impaired systolic function and compromised ejection fraction [23].

The remodeling of A-Kinase Anchoring Proteins (AKAPs) introduces another layer of complexity. AKAPs play a crucial role in spatially and temporally regulating PKA activity within the cell. Changes in the expression or localization of AKAPs observed in cardiomyopathies have the potential to disrupt the precise control of PKA signaling and its downstream effects [24].

Lastly, the Impact on Hypertrophic Signaling is noted in hypertrophic cardiomyopathies, characterized by abnormal growth of cardiac muscle cells. Dysregulated PKA signaling in this context can contribute to hypertrophic signaling pathways, influencing the delicate balance between hypertrophy and adaptive remodeling, as indicated by the research [25]. These alterations underscore the intricate role of PKA in maintaining cardiac homeostasis and how its dysregulation can contribute to the pathophysiology of cardiomyopathies [26].

4. Conclusion

In essence, this exploration into the world of PKA signaling and its connections to cardiomyopathies not only unveils the molecular intricacies of cellular regulation but also points toward promising avenues for therapeutic interventions. As our understanding of these complex interactions deepens, the potential for targeted treatments aimed at restoring the balance of PKA signaling in specific cardiomyopathies emerges, offering hope for improved outcomes and a more nuanced approach to cardiovascular health. Understanding these changes in the PKA signaling pathway in cardiomyopathies provides insights into the molecular mechanisms underlying disease progression. Targeting specific components of the PKA

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pathway may offer therapeutic opportunities for mitigating the adverse effects of cardiomyopathies, highlighting the potential for precision medicine approaches in the treatment of these complex cardiac disorders.

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