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GPCRs: Mechanosensing in Cardiovascular Health and Disease

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Abstract

Mechanosensitive G Protein-Coupled *Receptors* (GPCRs) are critical regulators in the cardiovascular system, translating mechanical forces like stretch, shear stress, and pressure into biochemical signals. These receptors, found in cardiomyocytes, endothelial cells, and vascular smooth muscle cells, govern essential functions from cardiac contractility to vascular tone. Their activation contributes to both adaptive physiological responses and pathological remodeling in conditions such as hypertension, atherosclerosis, and heart failure. Specific GPCRs, including AT1R, ET-1 receptors, aGPCRs, and GPR68, are key players in these processes. Understanding their diverse mechanotransductive mechanisms offers significant potential for developing novel therapeutic targets in cardiovascular disease.

Keywords

G Protein-Coupled Receptors; Mechanotransduction; Cardiovascular Disease; Cardiomyocytes; Endothelial Cells; Vascular Smooth Muscle Cells; Hypertension; Cardiac Remodeling; Therapeutic Targets

Introduction

The cardiovascular system is constantly exposed to mechanical forces, and G Protein-Coupled Receptors (GPCRs) emerge as pivotal mediators in translating these physical stimuli into biochemical signals. This mechanotransduction is essential for maintaining cardiac and vascular health, though it also contributes significantly to various pathological conditions.

This paper explores how mechanical forces in the heart, specifically stretch, activate G protein-coupled receptors (GPCRs) on cardiomyocytes. It details how this activation influences cardiomyocyte function, contributing to both adaptive responses and pathological remodeling in cardiovascular physiology. The research highlights the critical role of specific GPCRs in sensing these mechanical cues and initiating downstream signaling pathways [1].

This comprehensive review details the crucial role of GPCRs on endothelial cells in sensing mechanical stimuli, such as blood flow shear stress. It elucidates how these receptors act as mechanosensors, mediating diverse vascular responses to maintain vessel health or, conversely, contributing to the development of conditions like atherosclerosis and hypertension [2].

This study investigates how G protein-coupled receptors (GPCRs) in vascular smooth muscle cells (VSMCs) contribute to mechanotransduction, particularly in the context of hypertension. It reveals how abnormal mechanical forces, such as elevated blood pressure, can activate these GPCRs, leading to maladaptive vascular remodeling and disease progression [3].

This review offers a comprehensive discussion of various mechanosensitive GPCRs implicated in cardiovascular health and disease. It elaborates on how these receptors perceive mechanical

cues, such as stretch, shear stress, and pressure, and translate them into biochemical signals that profoundly influence cardiac function, vascular tone, and remodeling processes [4].

This paper highlights the Angiotensin II Type 1 Receptor (AT1R), a key GPCR, as a primary mechanosensor in cardiac cells. It details how mechanical stretch and pressure activate AT1R, leading to downstream signaling pathways that drive maladaptive cardiac remodeling, including hypertrophy and fibrosis, which are crucial in cardiovascular disease progression [5].

This paper delves into the critical role of Endothelin-1 (ET-1) receptors, which are GPCRs, in various vascular diseases. It suggests that ET-1 signaling, significantly influenced by mechanical cues like shear stress and vessel wall tension, contributes to pathogenic processes such as vasoconstriction, cell proliferation, and fibrosis, all relevant to the mechanotransductive environment of the vasculature [6].

This scoping review synthesizes current knowledge on mechanosensitive GPCRs and their involvement in the crucial processes of cardiac and vascular development. It highlights how mechanical forces are sensed by these receptors during embryogenesis, influencing cell fate decisions, tissue patterning, and the overall architectural formation of the cardiovascular system [7].

This paper explores the significant, yet often overlooked, role of adhesion G protein-coupled receptors (aGPCRs) in cardiac function. It details how these mechanosensitive receptors mediate cell-cell and cell-matrix interactions, influencing crucial processes such as cardiomyocyte proliferation, fibroblast activation, and extracellular matrix remodeling, contributing to both physiological cardiac processes and various cardiac pathologies [8].

This paper specifically investigates GPR68, a proton-sensing G protein-coupled receptor, and its mechanotransductive role within vascular smooth muscle cells. It demonstrates how GPR68 responds to mechanical stimuli, influencing critical cellular functions like proliferation and migration, and thereby significantly contributing to the development and progression of hypertension [9].

This very recent review provides an updated overview of mechanosensitive GPCRs in various cardiovascular diseases. It synthesizes current understanding of their diverse mechanotransductive mechanisms and thoroughly explores their significant potential as novel therapeutic targets for conditions like hypertension, atherosclerosis, and heart failure [10].

Description

The cardiovascular system is perpetually exposed to a complex array of mechanical forces, encompassing stretch, blood flow shear stress, and pressure. G Protein-Coupled Receptors (GPCRs) are indispensable cellular components that act as sophisticated mechanosensors, translating these physical stimuli into a cascade of biochemical signals, a fundamental process termed mechanotransduction [4]. This intricate signaling pathway is not only crucial for maintaining the precise equilibrium of cardiovascular health and function, but its dysregulation is also increasingly recognized as a significant contributor to the initiation and progression of various pathological conditions. Comprehensive reviews have meticulously detailed the emerging roles of these mechanosensitive GPCRs, providing a synthesized understanding of their diverse mechanisms in both physiological and pathological contexts [4, 10]. These versatile receptors perceive a wide spectrum of mechanical inputs, subsequently translating them into distinct cellular responses that profoundly influence critical aspects such as cardiac function, vascular tone, and remodeling processes across the myriad cell types resident within the cardiovascular system [4].

Within the cardiac milieu, mechanical forces, particularly direct stretch, are potent activators of GPCRs situated on cardiomyocytes, thereby significantly influencing their functional capabilities [1]. This activation goes beyond a simple reactive response; it actively participates in shaping both the adaptive physiological adjustments necessary for cardiac resilience and the maladaptive pathological remodeling frequently observed in various cardiovascular diseases [1]. A salient illustration is the Angiotensin II Type 1 Receptor (AT1R), a pivotal GPCR unequivocally identified as a central mechanosensor within cardiac cells. The activation of AT1R by mechanical stretch and pressure initiates a complex network of downstream signaling pathways that are directly implicated in driving adverse cardiac remodeling, including processes like hypertrophy and fibrosis, both of which are critical determinants in the inexorable progression of cardiovascular disease [5]. Furthermore, beyond the more extensively studied GPCRs, adhesion G Protein-Coupled Receptors (aGPCRs) represent an important, albeit sometimes underestimated, class of mechanosensitive receptors that exert significant influence over cardiac function. These receptors are crucial mediators of complex cell-cell and cell-matrix interactions, thereby impacting fundamental cellular processes such as cardiomyocyte proliferation, fibroblast activation, and the intricate remodeling of the extracellular matrix, collectively contributing to both the physiological function of the heart and the development of various cardiac pathologies [8].

In the vascular system, GPCRs located on endothelial cells function as critical mechanosensors, meticulously detecting mechanical stimuli such as the intricate forces of blood flow shear stress [2]. These receptors play a pivotal role in orchestrating a diverse range of vascular responses, which are absolutely essential for the maintenance of vessel integrity and overall vascular health. Conversely, any dysfunction or aberrant activation of these endothelial GPCRs can tragically contribute to the development of severe conditions, notably atherosclerosis and hypertension [2]. Similarly, vascular smooth muscle cells (VSMCs) are equipped with their own complement of GPCRs that are central to mechanotransduction, especially within the challenging context of hypertension. When exposed to abnormal mechanical forces, such as chronically elevated blood pressure, these VSMC-associated GPCRs can become activated, thereby precipitating maladaptive vascular remodeling and facilitating the relentless progression of disease [3]. Expanding on this, Endothelin-1 (ET-1) receptors, which are themselves GPCRs, are deeply implicated in a spectrum of vascular diseases. The signaling pathways mediated by ET-1 are profoundly influenced by prevailing mechanical cues, including shear stress and the tension within the vessel wall. This influence, in turn, contributes to a range of pathogenic processes such as sustained vasoconstriction, excessive cell proliferation, and detrimental fibrosis, all of which are highly relevant to the mechanotransductive environment of the vasculature [6]. Intriguingly, even proton-sensing GPCRs, exemplified by GPR68, have demonstrated a specific and crucial mechanotransductive role within VSMCs. GPR68 responds directly to mechanical stimuli, influencing critical cellular functions such as proliferation and migration, and thereby playing a significant part in both the initiation and progression of hypertension [9].

The profound involvement of mechanosensitive GPCRs extends beyond adult physiology and pathology, reaching into the foundational processes of cardiac and vascular development itself. A comprehensive scoping review meticulously synthesizes current knowledge, illuminating how these receptors intricately sense mechanical forces during embryogenesis [7]. This early mechanosensing is critical, profoundly influencing fundamental biological processes such as cell fate decisions, the precise patterning of tissues, and the overall architectural formation of the entire cardiovascular system [7]. This foundational and pervasive role underscores their overarching influence from the very earliest stages of development, continuing through adult physiological maintenance, and contributing to disease pathogenesis. The continuously evolving and increasingly sophisticated understanding of these diverse mechanotransductive mechanisms, along with the specific GPCRs involved, is now opening up remarkably promising avenues for targeted therapeutic intervention. Recent research and comprehensive reviews underscore the significant potential of identifying and modulating mechanosensitive GPCRs as novel therapeutic strategies for a wide array of cardiovascular diseases, encompassing hypertension, atherosclerosis, and heart failure [10]. Continued, focused investigation into these crucial receptors promises to unveil even more precise targets and intricate mechanisms, ultimately paving the way for more effective and personalized strategies to mitigate the progression of cardiovascular disease and improve patient outcomes.

Conclusion

G Protein-Coupled Receptors (GPCRs) are fundamental mechanosensors throughout the cardiovascular system, actively perceiving various mechanical cues like stretch, shear stress, and pressure. These receptors play a critical role in orchestrating cardiac function, vascular tone, and remodeling processes. This intricate mechanism influences both beneficial adaptive physiological responses and the harmful progression of diverse cardiovascular diseases. For example, mechanical stretch activates GPCRs on cardiomyocytes, profoundly impacting their function and contributing to pathological remodeling in the heart. Similarly, GPCRs located on endothelial cells function as key mechanosensors, responding to blood flow shear stress. This response mediates vital vascular adjustments necessary for maintaining vessel health, but can also contribute to the development of conditions such as atherosclerosis and hypertension. In vascular smooth muscle cells, GPCRs react to abnormal mechanical forces, like elevated blood pressure, initiating maladaptive vascular remodeling and disease progression. Specific GPCRs, such as the Angiotensin II Type 1 Receptor (AT1R), are recognized as central players in cardiac mechanotransduction, driving processes like hypertrophy and fibrosis when activated by mechanical stimuli. Other crucial GPCRs, including Endothelin-1 (ET-1) receptors and adhesion GPCRs (aGPCRs), are also deeply involved in vascular pathologies and cardiac function, respectively. Even lesser-known receptors like GPR68 demonstrate significant mechanotransductive roles in vascular smooth muscle cell function and hypertension. The collective research highlights the diverse mechanotransductive mechanisms of GPCRs, offering a promising avenue for novel therapeutic targets in cardiovascular diseases, including hypertension, atherosclerosis, and heart failure.

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