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Targeting the apelin axis: GPCR-directed peptide therapies for cardiovascular disease

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Abstract. G protein-coupled receptors (GPCR)play key roles in various physiological processes, especially in the regulation of cardiovascular function and morphology. The current share of peptide- and protein-antibody-based GPCR drugs is gradually increasing. Several studies have identified and understood the role of GPCR in vasodilatory regulation and cardiac function. In addition, some studies have explored the relationship between GPCRs and CVD-related physiological processes such as inflammation, thrombosis and vascular endothelial function. There is still a gap in the study of GPCRs in CVD in terms of a deeper understanding of the role of specific subtypes of GPCRs in the pathological process and their signaling mechanims, as well as how to develop specific drugs targeting these receptors to improve therapeutic efficiency and reduce side effects. This article will focus on important signaling pathways related to CVD. The potential applications and research progress of drugs such as Apelin-13 and MM07 in CVD therapy are particularly emphasized. This paper provides a reference for future research on the progress of GPCR in CVD. Future studies could focus on in-depth exploration of the signaling pathways of GPCRs, the development of more specific and safe drugs, and the study of new strategies for GPCRs in the prevention and treatment of CVDs

Keywords: Cardiovascular disease, GPCR, targeted therapy.

1. Introduction

GPCR, which stands for G protein-coupled receptor, is also recognized as the seven transmembrane receptors (7TMRs). These receptors play a pivotal role in various physiological processes, including cell growth and differentiation, immune system regulation, neurotransmission, and metabolism. The GPCR family is broadly classified into five subfamilies: Rhodopsin-A (Class A), Secretin-B (Class B), Metabotropic. C (Class C), Frizzled. F (Class F), and Adhesion-aGPCR.

The drugs that target GPCRs are typically categorized based on their structural characteristics: small molecules, peptides, and protein-antibody drugs. Furthermore, GPCR-targeting drugs can be classified by their functional mechanisms: Agonists, which initiate a biological response; Antagonists, which block receptor activation; Inverse Agonists, which reduce constitutive activity; and Allosteric

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Modulators, which alter receptor function through binding at sites distinct from the primary ligand-binding site.

From the point of view of drug forms, the share of peptide and protein-antibody drugs is gradually increasing. Among the GPCR drugs in the clinical stage, peptide drugs account for 11%, and in the marketed stage, the percentage is 5% [1]. Comparison of the morphology of GPCR drugs in the marketed and clinical stages reveals that peptide drugs have become a new trend in GPCR development. In the market phase, the majority of GPCR drugs are classified as either antagonists or agonists, representing a 95% share of the total GPCR drug landscape [1].

GPCR is widely expressed in the cardiovascular system and plays a key role in regulating cardiovascular function and morphology. Approximately one-third of all drugs currently available for the treatment of CVD target GPCRs [2]. This shows that the relationship between GPCR and CVD is very strong.

This paper integrates and summarizes current research findings on the role of GPCRs in CVD therapy to provide a comprehensive framework of knowledge for subsequent researchers. Currently, the FDA has approved 475 drugs targeting GPCRs, accounting for 34% of all approved drugs, 27% of the market share, and a market capitalization of $1 trillion in the last five years. Therefore, this paper can help research funding allocators understand research directions with high scientific and societal value.

2. Related pathway

2.1. PI3K/Akt

The Phosphoinositide 3-kinase (PI3K) and Akt pathway plays a crucial role in cell survival, proliferation, and metabolism. This pathway is also essential for myocardial cell protection and endothelial function. Activation of the PI3K/Akt pathway promotes cell survival and anti-apoptosis, thereby offering protective effects in CVDs such as heart disease and atherosclerosis.

2.2. Notch

The Notch signaling pathway plays a crucial role in cell fate determination, proliferation, and apoptosis. This pathway is also significant in vascular development, endothelial cell function, and CVDs such as atherosclerosis [3].

2.3. Wnt/β-cateni

The Wnt signaling pathway plays a critical role in cell growth, differentiation, and tissue regeneration. β-catenin is the core regulatory factor of this pathway [4]. The Wnt/β-catenin pathway is crucial for cardiovascular development, myocardial regeneration, and diseases such as atherosclerosis.

Biased agonism refers to the fact that in the case of activation of the same receptor, different ligands may lead to selective activation of specific signaling pathways, rather than activating all possible pathways at the same time. It can be used extensively.

The first is selective signal pathway activation, which allows different ligands to selectively activate specific signal pathways.

Then there is signaling pathway bias, which can lead to bias of signaling pathways by biasing agonists, so that signaling pathways are activated stronger or weaker, affecting intracellular physiological effects.

It can also be used as a drug design and therapeutic application, and biased agonism can help design more selective and specific drugs.

In terms of physiological and pathological mechanisms, the study of bias agonism is helpful for understanding the complexity of cell signaling and the role and influence of different signaling pathways in the occurrence and development of diseases.

As research intensifies and understanding of the structure and function of adrenergic receptors improves, scientists are looking for more selective drugs to minimise side effects and improve efficacy. New selective agonists targeting theα1 receptor subtype may reduce the effects on the heart muscle

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when treating hypertension. In addition, research on theβ3 receptor may lead to the development of new drugs for weight loss and the treatment of diabetes. In addition, studies of beta-3 receptors can pave the way for the development of new drugs for the treatment of weight loss and diabetes. Subsequent studies will show new processes of sympathetic adrenal system and give more precise objectives for clinical treatment. Future research will continue to reveal new mechanisms of the sympathetic-adrenal system and provide more precise targets for clinical therapy.

Angiotensin II receptors play a key role in the renin-angiotensin system (RAS), for which angiotensin II is the primary ligand. These receptors are known as GPCRs and are key components involved in the regulation of blood pressure, fluid balance, cell growth and apoptosis. Angiogenesis II receptors are mainly of two types called AT1 and AT2 respectively. These receptors have unique functions and means of signalling.

AT1 receptors are the primary receptors responsible for most of the physiological effects of Ang II. They cause vascular constriction, sodium and water delay, arterial pressure rise and inflammation by activating various intracellular signaling routes such as phosphatidilinozitol, proteinocinase c and quinine map. On the other hand, the function of AT2 receptors is less well defined, but studies suggest that they may be involved in the regulation of cell growth, tissue repair and apoptosis, sometimes producing effects opposite to those of AT1 receptors. At2 receptors transmit signals through several channels, including phosphate and calcium, which are channel-dependent [5].

In the field of drug therapy, receptor blockers for angiotenzin II (arb), directed at AT1 receptors, are widely used to treat hypertension, heart failure, chronic kidney disease and other diseases [6]. These drugs can effectively block the activation of AT1 receptors with angiotenzin II, thereby reducing its adverse physiological effects.

3. Apelin-13

Apelin is widely distributed in various tissues and cells in the human body. After purification, it can be divided into many different subtypes according to the amounts of amino acid in different polypeptides. Apelin-13 is highly expressed in adipose cells, vascular smooth muscle cells [7], endothelial cells and other cells in the cardiovascular system, and participates in processes such as angiogenesis, inflammation, apoptosis, autophagy, oxidative stress, etc. Apelin-13 has also been shown to be closely related to the physiological and pathological mechanisms of various cardiovascular systems. It mainly acts on APJ receptors to exert vasodilatation and inotropic actions, promote the release of vasodilators (principally nitric oxide), and then cause an increase in blood flow.

Early studies have found that although apelin exists in a variety of different peptides, pyroglutamylated apelin-13 is the main isomer of apelin in human heart and plasma [8]. In recent years, clinical trials have also evaluated the effects of [Pyr1] apelin-13 administration on the human cardiovascular system. A clinical trial reported in 2013 [9] found that infusion of [Pyr1]apelin-13 can effectively induce APJ receptor agonism in healthy volunteers and heart failure patients, improve peripheral vasodilation and cardiac output; and confirmed that the cardiovascular effects of [Pyr1]apelin-13 are local and systemic and sustained, and are not affected by activation of the renin-angiotensin system or heart failure disease, so it has the potential to be a new type of heart failure therapy. Another clinical trial reported in 2010 [10] measured the effects of acute administration of apelin on peripheral, cardiac, and systemic hemodynamic variables in healthy volunteers and patients with chronic stable heart failure, and found that short-term infusion of apelin caused peripheral and coronary vasodilation, increased cardiac output, and reduced cardiac preload and postload, confirming for the first time that apelin can improve myocardial contractility as a direct coronary vasodilator in humans. Although the acute infusion method used in this study can only prove the short-term effect of apelin and cannot explain whether there is a long-term APJ agonist effect in patients with chronic heart failure, it may still benefit patients with acute decompensated heart failure.

Overall, Apelin-13, as an Apelin isoform widely distributed in the vascular system, has been shown by many studies to play a significant protective role in the occurrence and development of vascular diseases. Future studies can focus on how to specifically regulate the efficient expression of Apelin-13

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from the genetic level, activation of signaling pathways, etc., so that it can play a more effective protective role in cardiovascular diseases.

4. MM07

Although [Pyr1] apelin-13 has shown good effects in clinical trials for the treatment of heart failure, in the process of studying the interaction between Apelin and its receptor APJ, researchers found that APJ is actually a dual functional receptor in cardiac hypertrophy. APJ can simultaneously accept and integrate protective signaling from apelin and pathological signaling from mechanical stretch stimuli by different mechanisms. The effects of APJ activated by balanced agonists such as apelin-13 not only have cardiovascular protective effects, but also lead to cardiomyocyte hypertrophy by enhancing β-arrestin recruitment while reducing G-protein signaling. Therefore, the subsequent apelin drug research goals are mainly to develop a selectively stimulating G-protein signaling while avoiding activating detrimental β-arrestin signaling pathway to prevent harmful cardiac hypertrophy.

After the publication of the above study, some researchers used molecular dynamics simulations of apelin/APJ interactions to design a novel [Pyr1] apelin-13 cyclic analogue and also an APJ biased agonist called MM07 [11]. The study showed that [Pyr1] apelin-13 increased peripheral vasodilatation and cardiac output while also causing significant hypotension and hemodynamic instability; MM07 also reduced vascular resistance but did not cause changes in blood pressure and heart rate. Compared with natural [Pyr1] apelin-13, MM07 showed similar or better effects than [Pyr1] apelin-13 in terms of pharmacodynamics and pharmacokinetic properties, such as longer half-life and lower β-arrestin pathway activation [12].

The development and research of MM07 have shown that APJ biased agonists selectively activate G-protein pathway but avoid activating the β-arrestin pathway, which may be a safer and more effective therapeutic strategy for the treatment of CVDs.

Since then, several studies have been conducted on the efficacy of MM07 for the disease of pulmonary arterial hypertension (PAH). In Sprague-Dawley rats with monocrotaline-induced or Sugen/hypoxia (SuHx) induced PAH, MM07 can reduce right ventricular hypertrophy and inhibit apoptosis of pulmonary artery endothelial cells. It also has functions beyond [Pyr1] apelin-13, such as weakening heart and pulmonary vascular remodeling and vessel muscularization [13], further confirming that biased agonists represented by MM07 have additional benefits from native non-biased agonists by altering differential downstream signaling. At the same time, since apelin-mediated pathway is independent of the standard-of-care drug Macitentan, it can be used as a potential adjuvant therapy or complementary therapy to the current standard treatment.

5. WN353 & WN561

Although the results of several novel biased agonists have shown reduced β-arrestin signaling, β-arrestin signaling that has not been completely eliminated will still lead to side effects such as heart failure and hypertrophy to a certain extent. Therefore, the development of complete restrained G-protein biased agonists is the main goal of future safe clinical application of Apelin/APJ-targeted drug. The researchers determined the complex structure of three agonists, apelin-13, MM07 and CMF-019, bound to the APJ receptor, combined with previous studies on the conformation of the APJ complex during β-arrestin activation, and identified two pivotal hotspots of APJ biased signaling. Subsequently, the researchers designed WN353 and WN561, two novel peptide analogs that eliminated β-arrestin signaling while retaining G protein signaling, based on the structure of the MM07 peptide.

In a cell model of pathological cardiomyocyte hypertrophy, WN353 and WN561 were able to significantly reduce the level of hypertrophic marker atrial natriuretic peptide (ANP) [14] compared with APJ agonists such as Apelin, MM07, and CMF-019. In addition, WN561 could also significantly reduce the level of another hypertrophic marker β-MHC/α-MHC and showed significantly greater stability than WN353 in both human plasma and cell culture medium. In a pathological mouse model, WN561 also profoundly ameliorated myocardial hypertrophy while other APJ agonists didn't.

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This study demonstrated that WN561 can significantly reduce myocardial hypertrophy in mouse models with and without pathological damage, indicating that fully G protein-biased APJ agonists are beneficial in eliminating the side effects caused by β-arrestin pathway activation, and also provides a reference for the subsequent design of other biased agonist structures

6. Conclusion

Despite the limitations of current clinical studies, the apelin axis remains a therapeutic target of great interest. From the perspective of GPCR drug development, this article provides a comprehensive analysis. The proportion of peptide/protein drugs targeting GPCRs is increasing. These peptide drugs represent a new trend in the field, reflecting their increasing importance and potential therapeutic benefits. Most GPCR-targeted drugs currently on the market are antagonists or agonists, accounting for 95% of such drugs. There is also a growing interest in drugs that act on non-traditional orthotopic sites, indicating that therapeutic strategies have gone beyond traditional mechanisms. GPCRs are crucial in various physiological processes, especially in cardiovascular regulation. They play a key role in the regulation of vasodilation, cardiac function, and other CVD-related processes such as inflammation, thrombosis, and endothelial function. Although significant progress has been made, there are still gaps in understanding the specific subtypes of GPCRs and their signaling mechanisms in the context of CVDs. Future research should focus on in-depth exploration of these pathways, the development of more specific and safer drugs, and the investigation of the potential application of GPCRs in the prevention and treatment of CVDs.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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