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Research Progress of Histamine and Its Receptors in Heart Diseases

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Abstract:

Cardiovascular diseases are the leading cause of mortality and are increasing in prevalence. These diseases encompass a range of conditions affecting cardiac structure and function, impairing blood supply, myocardial activity, electrical conduction, and valve performance, posing significant health risks. Histamine, traditionally used in gastric secretion testing and desensitization therapies, along with its receptor antagonists, such as H1 (H1R) and H2 (H2R) receptors, has gained attention for its role in cardiac remodeling and heart failure. This review explores the involvement of histamine and its receptors in myocarditis, myocardial infarction, heart failure, and myocardial fibrosis. H1R and H2R contribute to cardiomyopathy, hypertension, and heart failure through mechanisms like immune cell modulation, inflammatory mediator release, and cardiomyocyte regulation. H3R and H4R potentially affect cardiac function by modulating neurotransmitter release and influencing sympathetic and parasympathetic activity. While the role of H4R remains unclear, its connection to immunity and inflammation suggests promising therapeutic potential. Histamine receptors represent critical factors in the progression of heart diseases, offering insights into their pathophysiology and therapeutic applications. Despite recent advances, further research is needed to clarify their specific mechanisms and therapeutic targets. Understanding histamine receptor pathways could pave the way for innovative strategies in preventing and treating heart diseases, addressing a significant global health challenge.

Keywords:

Histamine
Heart disease
Myocarditis
Myocardial infarction

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1. Introduction

It is estimated that the total number of patients with cardiovascular diseases in China has exceeded 290 million, ranking first among the mortality rates of various diseases, and the incidence and mortality rates of heart diseases are showing an increasing trend year by year [1]. Heart disease is a general term for a variety of heart conditions caused by abnormalities in heart structure and function. These diseases can affect the blood supply to the heart, the contraction and relaxation of the myocardium, the electrical activity of the heart, and the function of the heart valves, posing a serious threat to human health [2]. Heart disease is one of the leading causes of death worldwide, so the prevention, diagnosis, and treatment of heart-related diseases are crucial. Histamine was originally used as an agent to examine gastric secretory function and desensitization (increasing doses of small injections). Its receptor antagonist, the histamine H1 receptor (H1R), is used for anti-allergy treatment, and the histamine H2 receptor (H2R) is used for gastric acid suppression therapy. It is currently known that histamine and its related receptors may be important factors in adverse cardiac remodeling and heart failure; although many reviews on histamine receptors have been published, there are few systematic reviews on the effects of histamine and its receptors on heart diseases and related mechanisms. Therefore, this review aims to discuss the role of histamine and its receptors in myocarditis, myocardial infarction, heart failure, and myocardial fibrosis, providing the latest developments in the study of histamine receptors on adverse cardiac remodeling and other heart-related diseases, further exploring the potential of targeting histamine receptors as a treatment for heart diseases and offering new perspectives for future research directions.

2. Overview of histamine and its receptors

In 1910, Dale and Laidlaw first revealed the existence of histamine, which is mainly synthesized by mast cells, basophils, platelets, histaminergic neurons, and enterochromaffin cells and stored in vesicles within these cells. When cells are stimulated, histamine is released and involved in regulating various biological processes. Under physiological conditions, the heart contains histamine, and its content varies depending on the heart chamber and species. The histamine content is typically highest in the right atrium, followed by the left atrium, right ventricle, and left ventricle. In the heart, histamine can be secreted by sympathetic nerves and mast cells, and its concentration is relatively high in mammalian cardiomyocytes [3].

As research and understanding of histamine continue to deepen, it has been discovered that there are four types of histamine receptors, namely H1R, H2R, histamine 3 receptor (H3R), and histamine 4 receptor (H4R), based on the chronological order of their discovery. All four histamine receptors are G protein-coupled receptors widely distributed throughout the body. It is known that H1R is mainly present in smooth muscle cells, endothelial cells, and neurons of the central nervous system; H2R is primarily expressed in gastric mucosa; H3R is expressed almost exclusively in the nervous system and plays a crucial role in various brain diseases; increasingly, evidence suggests that H4R is primarily associated with allergies, inflammation, and autoimmune diseases [4]. All four histamine receptors can exist in the hearts of mammals, but currently, H1R and H2R are the most extensively studied. In the cardiovascular system, H1R is primarily located on vascular smooth muscle, and histamine can cause vasodilation by activating H1R, potentially leading to hypotension and increased vascular permeability. H1R may also slow down heart rate through the conduction system of mammalian hearts, including human hearts. By activating H2R, histamine can increase heart rate and cardiac contractility and mediate adverse effects on cardiac remodeling by acting on cardiomyocytes, fibroblasts, and even endothelial cells. H3R and H4R are present in the neuronal cell structures of mammalian hearts but absent in cardiomyocytes [5]. This review summarizes the research progress and related mechanisms of histamine and its receptors in heart diseases, providing insights and research directions for exploring the diagnosis and treatment of heart diseases.

3. Histamine and heart diseases

3.1. Myocarditis

In 1998, Patella demonstrated elevated histamine levels in the myocardium of patients with idiopathic dilated

cardiomyopathy or ischemic cardiomyopathy. In 2004, Palaniyandi *et al.* found that interleukin-10 can inhibit myocardial damage by reducing histamine levels and suppressing mast cell degranulation, thereby preventing and treating acute myocarditis. In a mouse model of viral myocarditis induced by encephalomyocarditis virus, the use of the selective histamine H1R antagonist cetirizine significantly reduced the degree of myocardial fibrosis compared to the control group, delaying the occurrence of myocardial remodeling. In an experiment using a rat model of experimental autoimmune myocarditis (EAM), EAM rats were treated with selective H1R, H2R, H3R, and H4R antagonists. After observing myocardial damage, survival time, degree of fibrosis, and other ventricular function indicators, it was confirmed that the selective H4R antagonist provided the greatest benefit for EAM rats in preventing inflammation, reducing myocardial fibrosis, and delaying the progression to chronic heart failure. The selective H1R antagonist was the second most effective, while the selective H3R antagonist exacerbated myocardial fibrosis. The results of H2R treatment were more complex, possibly exhibiting a bidirectional regulatory effect on heart damage in EAM rats [6]. Further investigation into the efficacy and mechanisms of H4R antagonists in the treatment of myocarditis is of great significance and research potential.

3.2. Myocardial fibrosis

Activated mast cells are the primary source of profibrotic growth factors such as transforming growth factor β1 and fibroblast growth factor [7]. Histamine, as the main mediator of mast cells, has been shown to promote fibroblast proliferation in a dose-dependent manner. Compared to normotensive Wistar rats, the myocardial histamine content and H2R expression in spontaneously hypertensive rats increase with age. Treatment with the selective H2R antagonist famotidine significantly improves collagen content, myocardial fibrosis, left ventricular hypertrophy, and ventricular function in spontaneously hypertensive rats, with a comparable degree of improvement to that achieved with traditional β-blocker metoprolol treatment [8]. Male Wistar rats administered with 2 mg/(kg·d) of the anthracycline doxorubicin for five weeks develop heart fibrosis, thinning of the left ventricular wall, ventricular dilation, and impaired systolic and diastolic function. Blocking H2R with famotidine improves all these parameters [9]. In 2014, Leary *et al.* explored the role of H2R in adverse myocardial remodeling by performing aortic constriction on H2R knockout ($H2R^{-/-}$) mice. After four weeks, $H2R^{-/-}$ mice that underwent aortic constriction showed improvement in heart fibrosis and left ventricular hypertrophy. In 2023, Luo *et al.* found that in mouse models of ischemia-reperfusion or permanent occlusion, treatment with famotidine or in $H2R^{-/-}$ mice reduced the myocardial infarction size, while treatment with an H2R activator increased the infarction size. Gergs *et al.* [10] discovered that in the left atrium of H2R-overexpressing mice exposed to hypoxia and reoxygenation, the H2R-overexpressing mice had greater contractility during the 30-minute reoxygenation period compared to wild-type mice. Therefore, the release of histamine and activation of H2R may initially be a protective response to injury, increasing contractile function, but can be harmful in the long term, including increasing infarction size. Currently, there is limited research on the role of H3R and H4R in myocardial fibrosis, but it is believed that they may reduce myocardial fibrosis that occurs in heart failure. A recent study confirmed the expression of H3R on cardiac fibroblasts in mouse hearts, and activation of this receptor can antagonize the effects of angiotensin II, thereby reducing macrophage infiltration and improving myocardial fibrosis. However, blocking H3R has little effect on the occurrence of myocardial fibrosis and inflammation [11]. The specific mechanism of H3R in heart failure remains incompletely elucidated. In summary, histamine may have a dual role in myocardial fibrosis through H2R. Exploring the specific mechanism of H2R in myocardial fibrosis and the selection of treatment timing is of great significance. H3R and H4R may have the potential to treat heart fibrosis, but their specific mechanisms require further investigation.

3.3. Myocardial infarction

The mechanism of histamine's influence on myocardial infarction is highly complex. On one hand, histamine may contribute to myocardial infarction through mast cell infiltration within infarcted plaques [12]. On the other hand, histamine could be involved in the process of myocardial infarction and fibrosis via histidine decarboxylase [13]. Mice lacking histidine decarboxylase can exacerbate acute

myocardial infarction through neutrophil extracellular traps [14]. Both the H1R blocker chlorpheniramine and the H2R antagonist cimetidine have been shown to reduce histamine-induced collagen synthesis, thereby inhibiting post-infarction myocardial fibrosis. Ketotifen and ranitidine have also demonstrated similar effects [15]. Activation of histamine H2R can worsen ischemia-reperfusion injury by disrupting mitochondrial function and increasing cardiovascular endothelial cell permeability, potentially increasing the size of the myocardial infarction area and the degree of myocardial fibrosis. Selective H2R antagonists like famotidine can improve infarct size and myocardial fibrosis. The impact of H3R on myocardial infarction mainly manifests in two ways: first, activation of histamine H3R increases fibroblast collagen accumulation and the quality of collagen deposition in myocardial infarction scars, enhancing the degree of myocardial fibrosis to prevent the expansion of the infarction area or scar rupture [16]; second, H3R can inhibit sympathetic nerve transmission in the heart. H3R agonists attenuate the overactivation of the renin-angiotensin system and the sympathetic nervous system in a rat model of myocardial infarction, improving the integrity of myocardial tissue [17]. Additionally, H3R can mediate the downregulation of angiotensin receptor subtype 1 expression, thereby inhibiting the role of neuronal sodium-hydrogen exchanger 1 [18]. When a myocardial infarction scar is about to rupture, H3R promotes myocardial fibrosis and scar formation to prevent further expansion of the infarct size. During ischemia/reperfusion, H4R on the membranes of cardiac mast cells exhibits a cardioprotective anti-renin-angiotensin system effect, including reducing the release of renin and norepinephrine and alleviating reperfusion arrhythmias. Furthermore, similar to H3R, H4R, which is present in cardiac sympathetic nerve endings, can also inhibit the release of norepinephrine. Experimental models of myocardial ischemia in animals also result in increased histamine release. A small prospective clinical study showed that adding the H1R blocker loratadine to the standard anti-ischemia regimen improved ischemia parameters on a 12-lead electrocardiogram during exercise tolerance testing for patients with acute myocardial infarction. In this study, 10 patients received loratadine for seven days and showed improvement in maximum ST-segment depression, the number of leads with ST-segment depression, and ST-segment depression recovery time. These benefits tended to decrease after stopping loratadine. A second group of patients did not receive loratadine within one week of acute myocardial infarction and then started oral loratadine on day seven; this group still showed improvement in ischemia parameters. The study attributed the beneficial effects of loratadine to its ability to counteract post-infarction coronary artery constriction. In summary, in models of myocardial infarction, the activation of H1R and H2R promotes myocardial fibrosis, and antagonizing their activation helps improve the condition of patients with myocardial infarction. H3R and H4R may play a “protective” role in the body, but the specific mechanisms need to be further elucidated, presenting research prospects for the treatment of patients with myocardial infarction.

3.4. Heart failure

According to statistics, there are approximately 26 million patients with heart failure globally, with a one-year mortality rate ranging from 17% to 45%. Patients in low- and middle-income countries have worse outcomes [18]. Histamine can promote the occurrence and development of heart failure, and when histamine concentrations decrease, this process can be delayed or even blocked. Currently, there is limited research on the role of H1R in heart failure, which may be related to the predominant distribution of H1R in the coronary vasculature. However, a study on leptin receptor-deficient female mice treated with cetirizine demonstrated reduced vascular leakage, leukocyte infiltration, and end-diastolic pressure, confirming that the H1R antagonist cetirizine can improve diastolic dysfunction in heart failure with preserved ejection fraction [3]. Numerous studies have shown that activation of H2R increases mitochondrial permeability in cardiomyocytes and induces cardiomyocyte apoptosis [19]. It has also been confirmed that using selective H2R antagonists or knocking out the *H2R* gene significantly improves cardiomyocyte apoptosis and fibrosis. The use of H2R blockers can also promote morphological recovery of the right ventricle and reduce mortality in critically ill patients with heart failure [20]. The large-scale Atherosclerosis Risk in Communities (ARIC) study, a prospective study that recruited participants aged 45 to 84 from six communities in the United States

between 2000 and 2002 and followed them for 10 years, found that the use of H2R antagonists reduced the risk of heart failure by 62% [21]. Therefore, this study suggests that early, long-term, and continuous use of H2R antagonists has the potential to provide special benefits to patients with heart failure.

H3R and H4R can inhibit the release of norepinephrine from storage sites (ganglia) in the human heart. H3R is primarily located on histaminergic neurons in the brain. Activation of H3R can reduce the release of norepinephrine in both normal and ischemic heart conditions, potentially helping to reduce stress responses and damage to the heart. Additionally, heart failure is often associated with a chronic inflammatory state, and H3R may primarily exert its effects on the heart by modulating inflammatory responses. H4R is mainly involved in the body's immune response, particularly in innate immunity. Heart failure patients often experience activation of the immune system and inflammatory responses, and H4R may influence the progression of heart failure by modulating the function of immune cells. A 2022 study by Zhang *et al.* showed that activation of H4R can inhibit the expression of certain proinflammatory cytokines while increasing the expression of anti-inflammatory cytokines such as interleukin-10, which may be beneficial for patients with heart failure. The potential mechanisms and therapeutic potential of histamine receptors in heart failure are gradually being elucidated, but more research is needed to clarify their specific roles and mechanisms in the treatment of heart failure.

4. Conclusion

Histamine and its receptors play crucial roles in the development and progression of heart diseases. H1R and H2R primarily contribute to cardiomyopathy, hypertension, myocardial infarction, and heart failure. Based on existing research, it can be speculated that histamine receptors may have the following mechanisms in the heart: H1R may affect inflammatory processes by modulating the activation of immune cells and the release of inflammatory mediators; H2R may influence myocardial contraction and relaxation by regulating cardiomyocyte function; and H3R and H4R may affect sympathetic and parasympathetic nervous system activity by modulating neurotransmitter release. Although the role of H4R in heart diseases remains unclear, its involvement in innate immunity and inflammatory responses may offer new strategies for treating heart diseases. In recent years, the role of histamine and its receptors in the development and progression of heart diseases has become a research hotspot, but further investigation is needed to elucidate their specific mechanisms and targets in heart diseases.

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