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Association between Expression Levels of Phenylacetoglutamine and Heart Failure

Luofei Huang[1,a,*]

[1]*Shanghai University, Shanghai, 200444, China*
a. huangluofei0512@qq.com
**corresponding author*

Abstract: Cardiovascular disease poses a significant health challenge globally, with heart failure being a common and often fatal endpoint for many cardiac conditions. Despite advances in medical science, the mortality rate among heart failure patients remains distressingly high, largely due to the absence of superior diagnostic and therapeutic tools. Phenylacetylglutamine, an active metabolite generated by intestinal microbes, is acknowledged as being linked to the progression of cardiovascular diseases. Therefore, through a comprehensive literature review, this paper explores the correlation between phenylacetylglutamine levels and heart failure levels, the correlation between phenylacetylglutamine and heart failure markers, as well as summarising the impact of phenylacetylglutamine on the prognosis of heart failure patients. By synthesizing and analyzing current research, this study aims to elucidate the relationship between PAG expression levels and heart failure and its underlying mechanisms. These findings contribute to the body of knowledge and may provide new insights and approaches to novel diagnostic and therapeutic strategies for treatment heart failure.

Keywords: phenylacetylglutamine, Heart failure, Gut microbiota, Cardiovascular disease, treatment

1. Introduction

Cardiovascular disease (CVD) is the leading cause of mortality in rich countries and is on the rise in developing countries as well. One in three deaths will globally be due to cardiovascular diseases[1]. Common cardiovascular diseases include coronary heart disease, myocarditis, hypertension, etc. Congestive heart failure (CHF) represents the terminal phase of numerous cardiac conditions. It signifies that the heart's ability to pump is compromised, resulting in an inadequate cardiac output that fails to satisfy the fundamental metabolic requirements of the body's tissues and organs[2]. The pathophysiological mechanism of heart failure is intricate, involving a myriad of factors, targets, and pathogenic mechanisms, that complicate its management. At present, the lack of effective diagnostic and therapeutic options for is starkly reflected in the high mortality rate, with 50% of patients succumbing within five years of diagnosis [2]. Therefore, vigorously investigating the etiology of heart failure and identifying novel therapeutic targets is of paramount importance. Such efforts could revolutionize the current landscape of HF management, potentially reducing its incidence and mortality rates, and ultimately, enhancing patient prognosis.

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In addition, the gut microbiota is tightly linked to the body's health, with the human gastrointestinal tract housing a vast community of microorganisms that assist in a multitude of physiological and biochemical processes. The gut microbiota carry out a multitude of roles in the human body, such as breaking down nutrients, establishing an intestinal epithelial barrier, modulating immune function, synthesizing vitamins and hormones, and generating metabolites that interact with the host. In recent years, it has become widely recognized that metabolites originating from the gut microbiota can impair gut function, thereby leading to a variety of diseases [3]. The gut microbiota is associated with a variety of human diseases, including cardiovascular disease. Studies on gut microbiota transplantation, specific pathways dependent on gut microbiota, and their downstream metabolites has shown that they can impact host metabolism and cardiovascular diseases, sometimes via known host receptors [4]. Gut microbes can interact with the host through multiple pathways, which are intimately involved in the onset and progression of heart failure, but current relevant research is not deep enough. Therefore, in order to further understand how the gut microbiota affects the occurrence of cardiovascular disease, it is critical to explore the activity of metabolites produced by the gut microbiota, their association with clinical phenotypes, and their association with hormones. Phenylacetylglutamine (PAGln) is one of the active metabolites produced by gut microbiota. In recent years, it has attracted the attention of many scholars. In the host, PAGln is involved in the pathogenesis of inflammation, platelet activation and other pathophysiological processes. Research has indicated that PAGln is implicated in the incidence of major adverse cardiovascular events and can serve as the potential biomarker for the prognosis of cardiovascular diseases. But few studies have investigated the correlation between PAGln expression level and heart failure [2].

This paper mainly analyzed and summarized the research progress of PAGln and heart failure in recent years, and reviewed the correlation between PAGln expression level and heart failure and its possible therapeutic means and effects. The aim is to offer novel insights and methodologies that could revolutionize the diagnosis and treatment of heart failure in the future, enhancing our approach to managing this critical health condition.

2. PAGln

2.1. Gut microbiomes dependent metabolite

PAGln is a metabolite dependent on gut microbes. Its production is mainly related to the necessary amino acid phenylalanine. The body is unable to synthesize on its own and must be ingested through dietary sources such as eggs, meat, and dairy products. Phenylalanine is the initial substrate for PAGln synthesis. After phenylalanine obtained from food enters the digestive tract, it is first converted to phenylpyruvic acid (PPY) by intestinal flora. Phenylpyruvate is further metabolized by gut microbiota to phenylacetic acid (PAA). There are two main pathways: the formation of phenylacetyl-coa catalyzed by reductase and the formation of phenylacetaldehyde catalyzed by phenylpyruvate decarboxylase to generate phenylacetic acid. After phenylacetic acid is generated, it enters the human blood circulation through the portal vein. In the liver, phenylacetic acid is combined with glutamine in the action of hepatic enzymes to produce phenylacetyl glutamine. In humans, PAA primarily conjugates with glutamine in the liver and kidney to form PAGln, while in rodents, it mainly conjugates with glycine to form phenylacetylglycine [3].

2.2. PAGln and development of heart failure

Studies have demonstrated that changes in PAGln levels are associated with the occurrence and progression of heart failure. Zhang et al. selected 58 patients with heart failure and 22 healthy volunteers as the control group [5]. Among 58 patients with heart failure, 29 patients were NYHA

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class III and 29 patients were NYHA class IV CHF according to the New York Heart Association (NYHA) cardiac function classification. The level of PAGln in the patient's plasma was measured by high performance liquid chromatography (HPLC), and the species and diversity of gut microbiota were determined by 16S rRNA sequencing [5]. The study revealed that plasma PAGln concentrations were markedly higher in patients with chronic heart failure than in healthy controls. The higher the severity of heart failure in patients, the higher the level of PAGln in plasma. In addition, the diversity of the gut microbiota was identified to decrease significantly in patients with heart failure by comparison to healthy controls, suggesting a change in the structure of the gut microbiota. This alteration suggests that the normal function of intestinal flora in patients with heart failure is damaged, and the flora may shift and proliferate, which may cause increased endotoxin release, induce infection or aggravate inflammatory response. The research indicates that the normal composition and distribution of the gut microbiota is altered by heart failure, which in turn alters PAGln levels in patients with heart failure.

Aiming at correlations between PAGln pair and different degrees of heart failure, Han et al. selected 100 patients with heart failure and divided them into mild CHF group (grade i - ii, $n = 50$) and severe CHF group (grade iii-iv, $n = 50$) according to the New York Heart Association (NYHA) cardiac function classification [6]. And 50 healthy volunteers were selected as the control group. A double antibody one-step sandwich enzyme-linked immunosorbent assay (ELISA) was conducted to measure PAGln levels in plasma. According to the analysis of the experimental results, the level of PAGln was positively correlated with the severity of heart failure. Notably, the level of PAGln in patients with severe heart failure are higher than those with mild heart failure. In addition, phenylethylglutamine has been demonstrated to correlate with different degrees of heart failure, Current studies have basically confirmed that phenylacetoglutamine is positively correlated with the severity of heart failure.

Patients with heart failure have significantly higher levels of PAGln than healthy subjects. Moreover, its content is positively correlated with the severity of heart failure.

2.3. The mechanisms of PAGln affecting heart failure

Romano et al. explored the clinical and mechanistic relationship between PAGln and heart failure (HF) [7]. The level of PAGln was correlated with the presence and severity index of HF in a dose-dependent manner, and the increase of PAGln was correlated with the decrease of subclinical indexes of left ventricular systolic function and myocardial strain in a dose-dependent manner. The effects of PAGln on cardiac fibroblasts in culture and HF-related cardiovascular phenotypes in vivo were also examined. It was discovered that PAGln, along with its derivative PAGly, could rapidly induce the expression of the cardiac BNP gene [7]. Moreover, the effect of epinephrine was significantly attenuated when the cardiomyocytes were treated with epinephrine and phenylacetoglutamine together. However, the myocardial cells did not respond significantly when PGLN was used alone, which may be due to the fact that PGLN may attenuate the positive inotropic effect of epinephrine by interacting with adrenergic receptors. In the presence of sympathetic stimulation, PAGln promotes negative inotropic effects that can cause the development of heart failure.

Fu et al. demonstrated that raised levels of PAGln may increase susceptibility to ventricular arrhythmias in mice with heart failure [8]. The heart failure model was induced by thoracic aortic coarctation (TAC), followed by intraperitoneal PAGln injections, which was measured by liquid chromatography-tandem mass spectrometry. Cardiac electrophysiological parameters were measured by electrocardiogram and programmed electrical stimulation in isolated hearts. It was found that the elevated level of PAGln led to the occurrence of cardiac inflammation and fibrosis in

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heart failure mice, which further led to the deterioration of cardiac function. In isolated heart perfused mice with cardiac failure, the action potential repolarization time was prolonged, the effective refractory period was shortened, and the arrhythmia was induced.

Furthermore, PAGln has been found to activate the TLR4/AKT/mTOR signaling pathway, so it is suggested that PAGln may enhance the susceptibility to arrhythmia after heart failure by activating this signaling pathway. Although PAGln is implicated in the occurrence and progression of heart failure through a variety of pathways, current research on its precise role is limited. The specific mechanism of PGLN's action on heart failure is currently unknown, and it may affect heart failure through multiple pathways.

2.4. Predictive effect and prognosis

Exploring the predictive and prognostic of PAGln in heart failure can offer new therapeutic concepts and methods for heart failure treatment. Zong et al. used liquid chromatography-tandem mass spectrometry to determined the PAGln level in plasma of 956 subjects, and followed up 471 subjects with stable chronic heart failure [9]. Logistic regression analysis was used to evaluate the association between PAGln and the risk of heart failure and PAGln. The results of this study showed that PAGln has a certain correlation with heart failure, and the increase of PAGln level will increase the risk of death in patients with heart failure,so PAGln can be used as a valuable index to predict the development of HF. In addition, Wei et al. measured plasma PAGln by liquid chromatography to explore the association between plasma PAGln levels and the incidence of adverse cardiovascular events and its prognostic effect [10]. They also examined the relationship between PAGln and the classical biomarker N-terminal pro-B-type natriuretic peptide (NT-proBNP) and the use of β-blockers. PAGln has a certain predictive value, and the simultaneous evaluation of PAGln and NT-proBNP levels can enhance the risk stratification of patients with heart failure. PAGln has a certain prognostic value when low NT-proBNP level is at a low level. However, no association was found between PAGln and β-blocker use. Also, Wang et al. selected 90 patients with heart failure, and used high performance liquid chromatography to detect serum trimethylamine oxide (TMAO) and serum PAGln, while also collecting ECG parameters [11]. This study took CHF patients complicated with atrial fibrillation (AF) as the dependent variable. Through data analysis, it was found that serum PAGln, serum TMAO and P-wave dispersion (Pd) were risk factors for CHF patients complicated with AF. In patients with heart failure, increased levels of PAGln may aggravate the deterioration of heart health. It is believed that the detection of phenylacetoglutamine level is helpful to evaluate the risk of atrial fibrillation in patients with heart failure.

In order to explore the prognostic value of PAGln in patients with heart failure, Tang et al. followed up a large number of patients with heart failure and found that patients with higher levels of PAGln had higher hospitalization and mortality within five years [12]. PAGln was found to be independent of traditional cardiac risk factors and cardiorenal risk markers. It is correlated with the adverse consequences of the prognosis of patients with heart failure, and has certain prognostic value. PAGln has great potential and research value in the prediction and prognosis of heart failure. Moreover, Yi et al. designed experiments based on conditions in which Dengzhanshengmai (DZSM) capsule may improve heart failure to explore the mechanism of action [13]. Experiments found that DZSM can considerably reduce systemic inflammation, improve intestinal barrier functions and enhance cardiac functions in HF rats. Further investigations discoverd that the beneficial effects of DZSM had relationship with the reduction of gut microbiota metabolite PAGln (PAGln) levels in serum and heart tissue. It has been suggested that DZSM can be used to reduce levels of PAGln to improve heart failure.

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In conclusion, the elevated level of PAGln may be used as a predictor of heart failure. At the same time, the high level of PAGln may affect the prognosis of patients. Using drugs to reduce its content can play an effective role in the treatment of HF.

3. Conclusion

At present, there is no good treatment for heart failure, so it is very important to explore new markers, intrinsic mechanisms, and treatment methods related to heart failure. Gut microbiota is closely related to the occurrence and development of heart failure. As one of the active metabolites produced by gut microbes, phenylacetoglutamine has been shown to be related to the severity of heart failure in many studies. However, the current research on this area is not sufficient and comprehensive, and it is not clear how PAGln in particular affects heart failure and the exact mechanism of action. The correlation between the expression level of PAGln and heart failure and the mechanism of action need to be further studied. Research in this field may be of great significance and value for improving the quality of life of patients, extending the life span of patients and promoting medical progress. The major limitations of this study is the lack of the demonstration of actual experiment and empirical research. The complete accuracy and reliability of the data cannot be guaranteed. There are also shortcomings in the data that can be collected.

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