Circulation: Heart Failure

EDITORIAL

Phenylacetylglutamine From the Gut Microbiota: A Future Therapeutic Target in Heart Failure?

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Accumulating evidence is suggesting a role of the gut microbiota in heart failure (HF). Several studies have demonstrated changes in the gut microbiota composition and function in patients with HF compared with healthy controls. However, the mechanistic pathways and the direction of the association has been unclear.[1]

See Article by Romano et al

In recent years, by utilizing unbiased high throughput studies, microbial metabolites that confers prognostic information in patients with cardiovascular disease (CVD) including HF have been identified. Importantly, these metabolites predict future risk of cardiovascular events independent of traditional risk factors, and through series of experimental studies, some of these metabolites have been implicated in the pathophysiology of HF initiation and progression.[2,3] In particular, the diet- and microbiota-dependent metabolites trimethylamine N-oxide (TMAO) and phenylacetylglutamine have shown promise as novel biomarkers and may ultimately present as potential treatment target in CVD.

TMAO is a metabolite produced following bacterial degradation of nutrients containing L-carnitine, choline, or phosphatidylcholine. Upon digestion, the gut microbiota produces trimethylamine, which is oxidized by the liver to TMAO. In mouse models, TMAO supplementation caused accelerated atherosclerosis.[4] In large human studies, circulating TMAO levels have been associated with prognosis and severity in CVD, including HF, acute coronary artery disease and ischemic stroke.[5] In subsequent studies in HF, TMAO has been associated with poor prognosis and adverse remodeling by exacerbating cardiac fibrosis.[6]

Phenylacetylglutamine is widely known as a uremic toxin and accumulates in children with urea cycle disorders. Similar to TMAO, it is mainly a bacterial degradation product, derived from phenylalanine rich food and undergoes subsequent conjugation with glutamine in the liver. Phenylacetylglutamine has previously been associated with the risk of ischemic stroke, atrial fibrillation and have strong association to chronic kidney disease.[2,7] The link between phenylacetylglutamine and CVD was first established by the same research group utilizing untargeted metabolomics. In that study, phenylacetylglutamine was associated with prevalent CVD, and the risk of developing major adverse cardiovascular events over the time course of 3 years. The investigators also demonstrated that the gut microbiome contributes to circulating levels of phenylacetylglutamine, and further experiments revealed that phenylacetylglutamine could enhance platelet adhesion and thrombus formation through interaction with a variety of G-coupled receptors, including adrenergic receptors.[2]

In this issue of the journal, Romano et al[8] report novel data regarding the clinical and mechanistic relationship of phenylacetylglutamine in HF. For the clinical part of the study, they utilized a US discovery cohort (n=3256) and a European validation cohort (n=829). They confirmed that subjects with prevalent HF had higher levels of phenylacetylglutamine, independent of the presence of coronary artery disease, CVD risk factors and importantly renal function. Furthermore, they elegantly showed that phenylacetylglutamine was associated with measures of cardiac function and severity, namely NT-proBNP (N-terminal pro-B-type natriuretic peptide) and left ventricular ejection

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fraction, in a dose dependent matter. The association with NT-proBNP, was also present in subjects devoid of HF. In line with this finding, phenylacetylglutamine has previously been associated with future risk of coronary artery disease in the setting of primary prevention, highlighting the potential use as an early risk marker for CVD.[9]

In the experimental part of the study, phenylacetylglutamine caused increased expression of the BNP gene *Nppb* in cardiomyoblasts from rats in vitro, and acute infusion of phenylacetylglutamine in mice increased *Nbbp* expression in the left atrium. Next, a negative inotropic effect on cardiomyocytes was demonstrated, but only in the presence of adrenalin. HF phenotypes have previously been shown to be inducible in experimental animals through injection of proinflammatory cytokines, provoking a negative inotropic response.[10] This has led to a widespread hunt for effective anti-inflammatory interventions, albeit few have been successful. Here the authors present another potential pathway, which holds fascinating therapeutic potentials either by targeting the effect of phenylacetylglutamine on the cardiomyocytes by antagonists, or by inhibiting its production in the gut.

As phenylacetylglutamine is microbiota-dependent, it is important to further characterize the HF-related changes in the gut microbiota which could interfere with phenylacetylglutamine production. The current study did not include any data on potentially associated changes in the gut microbiota composition or function. However, phenylacetylglutamine has previously been shown to be negatively correlated with several gut microbial families such as Lachnospiraceae and Bifidobacteriaceae, both of which are known short-chain fatty acid producers. Paradoxically, phenylacetylglutamine was also positively correlated with gut microbiota diversity, a widely used marker of a healthy gut, thus emphasizing a knowledge gap in connecting circulating phenylacetylglutamine levels to HF-related gut microbiota alterations.[9]

There are several unanswered questions. On the experimental side, how does phenylacetylglutamine influence HF models in vivo? And although the effect of phenylacetylglutamine in the initial CVD study was shown to be mediated via several adrenergic receptors on platelets, the exact molecular mechanisms are not shown here. On the clinical side, phenylacetylglutamine seems like a promising biomarker in CVD including HF. The direct involvement in disease makes it particularly interesting, since it provides a potential for classification of patients into, for example. high phenylacetylglutamine and low phenylacetylglutamine groups, forming a basis for treatment options. This would require further independent validation of its biomarker abilities in different populations, as well as proper clinical level assays and supporting data related to intraindividual stability over time. Furthermore, the clinical cohorts included were dominated by patients with high cardiovascular risk burden. The discovery of phenylacetylglutamine was initially made in a cohort with high risk of coronary artery disease, and thus it is an unanswered question whether the proposed effect of phenylacetylglutamine in HF is also relevant in non-ischemic HF, although some data in the current study suggest so.

The study nicely shows that phenylacetylglutamine could be a potential therapeutic target in HF. While waiting for pharmaceutical strategies to target phenylacetylglutamine, could we advise patients with HF to avoid phenylalanine rich foods to avoid high levels of phenylacetylglutamine? As an example, the artificial sweetener aspartame, a peptide rich in the phenylacetylglutamine precursor phenylalanine, has recently been reported to associate with risk of cardiovascular events.[11] According to American Heart Association/American College of Cardiology/Heart Failure Society of America guidelines for management of HF, healthy dietary patters are recommended for patients at risk of HF (stage A). Food based on animal protein seems to act as precursor for both phenylacetylglutamine and TMAO, and diets such as DASH (Dietary Approaches to Stop Hypertension) or the Mediterranean diet have been associated with a reduction of cardiovascular risk. However, urinary output of the microbial metabolites TMAO and phenylacetylglutamine have both been shown to be paradoxically increased in subjects with high adherence to the Mediterranean diet compared with low adherence.[12] To complicate things further, both metabolites undergo enzymatic modification in the liver and are dependent on renal excretion. Individual enzymatic activity may play a role for the circulating levels and should be explored in future research in this area.

Although promising, we are still in need of more studies exploring the use of phenylacetylglutamine as a biomarker in HF, but also in other populations, as well as further experimental characterization of the molecule and its effect. As an example, adrenergic receptors are not exclusive to the cardiovascular system, which was highlighted by the fact that phenylacetylglutamine also has been associated with the risk of developing lethal prostate cancer, possibly through the effect of beta adrenergic signaling on cancer cells.[13]

The present study provides encouraging evidence that phenylacetylglutamine could be more than an innocent bystander in HF. To further strengthen the case, there is a need of effective pharmacological agents to block or decrease levels of phenylacetylglutamine, in order to examine the effect of such blockade on cardiac remodeling and ultimately prognosis.

ARTICLE INFORMATION

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Disclosures

None.

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