Universe Scientific Publishing

Trimethylamine-N-Oxide: Its Role in Cardiovascular Disease, Mechanism and Potential Therapeutic Targets

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Abstract: Cardiovascular disease (CVD) is a common circulatory system disease and the collective name of all kinds of heart diseases, such as rheumatic heart disease, congenital heart disease, hypertensive heart disease and so on. According to WHO's publishment, CVD is the top three leading cause of death in the world. Therefore, it is necessary to study the risk factors of CVD. In recent years, there has been increasing research on the effect of diet on CVD, and red meat caught the attention of researchers. L-carnitine in red meat can eventually be oxidized to trimethylamine-n-oxide (TMAO) by the gut flora. In this review, I give evidence-based conclusions about the relationship between L-carnitine and CVD, metabolism of TMAO in the presence of intestinal microorganisms. I also discuss the mechanism by which TMAO increases the CVD risk and possible therapeutic targets offered by TMAO. Overall speaking, it is a promising research direction to find therapeutic targets by blocking L-carnitine's formation.

Keywords: Cardiovascular Disease; Trimethylamine-N-Oxide; L-Carnitine; Therapeutic Targets

Introduction

With economic development, the red meat diet has reached a high point in the developing world, and overconsumption of this diet has been linked to an increased risk of CVD [1]. L-carnitine, which is abundant in red meat, is digested by gut bacteria to produce two metabolites, trimethylamine (TMA) and TMAO. According to clinical research, L-carnitine has a positive inotropic effect on the heart and can improve the state of ischemia and hypoxia of myocardial cells [2]. However, TMAO is one of the crucial factor in the occurrence and development of CVD, such as AS and stroke . Although the mechanism between TMAO and CVD remains highly uncertain, some studies suggested that elevated plasma TMAO levels may lead to an increased risk for some adverse cardiovascular reactions, such as arrhythmia and myocardial ischemia. TMAO, as an important intestinal microbiota metabolite, Its formation can be effectively promoted by an intestinal bacteria called E.timonensis . What's more, Hazen and his colleagues identified a gene cluster—"gamma-butyrobetaine utilization" (gbu), which plays a critical role in the metabolic process of TMAO. So there are many potential therapeutic targets in the metabolic pathway of L-carnitine conversion to TMAO that are worth investigating.

1. Possible role of L-carnitine in CVD

L-carnitine is an amino acid, which can change fat into energy, which mainly comes from red meat, can balance cardiac energy metabolism by promoting mitochondrial oxidation. It is believed that L-carnitine has benefits for cardiomyopathy. The cardioprotective mechanism of L-carnitine has a connection wtih the reduction of the oxidative stress response, inflammation, and necrosis in cardiogenic cells. The meta-analysis shows that L-carnitine can reduce the area of myocardial infarction and relieve angina pectoris symptoms, helping diminish the mortality rate[3].

Ventricular remodeling is mediated by kappa B(a nuclear factor), and L-carnitine can restrain the abilities of some oxidases that control the procession. What's more, an animal experiment suggested that L-carnitine can reduce some main manifestations of arrhythmia, including eliminating abnormal cardiomyocyte discharge and atrioventricular nodal reentrant tachycardia and tachycardia. Some studies have shown that L-carnitine has a protective role in the heart and against heart failure, but its specific links with other physical organs stay unrevealed. Thus, more in-vitro trials with L-carnitine need to be conducted, leading to figuring out the mechanism underlying their correlation.

2. TMAO metabolism

TMAO is an metabolite of intestinal flora, compounded in the human's liver, and the generation of precursor TMA is inseparable from the intestinal microbiota. Some intestinal flora can produce TMA lyase, which converts choline, betaine, carnitine, and TMAO from direct dietary intake or indirect production into TMA[4]. With hydrophobic and hydrophilic double groups, TMAO can regulate protein activity and stability, increase foam cell formation and inhibit cholesterol reverse transport.

Precursors to TMA production include TMAO, carnitine, gamma-butylbetaine, croton betaine, and so on.

E.timonensis can effectively promote the conversion process in the bowels of the busymen, while that ability is weaker in the vegetarian gut due to the lower abundance of the E.timonensis. Additionally, researchers used samples and clinical data collected from patients followed for three years, then they founded that plasmaγBB levels are positively associated with CVD risk andγBB can modulate the expression level of gbu (six-gene cluster) which is crucial for TMAO metabolism[2].

3. TMAO and CVD risk

High levels of TMAO may be a new risk factor for CVD. However, some other research indicates that TMAO levels may not be associated with CVD. So in my view, the relationship between TMAO and CVD may be more complicated than that, and the uncertainty is strong, so using TMAO phenotype to identify CVD risk needs to be cautious.

Heart failure (HF) is an end-stage manifestation of CVD, and some recent evidence indicates that TMAO, may contribute to HF. In 2013, based on an untargeted metabolomics analysis of 4407 patients undergoing coronary angiography, researchers put forward that TMAO levels predicted an increased risk of CVD for the first time[5]. It seems that elevated TMAO levels can be a warning sign of CVDs, but is it the whole truth? I'm afraid not. A random trial showed TMAO circulated rapidly in the blood and was mostly excreted in the urine, in other words, TMAO didn't stay in plasma for so long, which was quite different from the elevated TMAO concentrations in AS patients and animal models of CVD[6].

4. Potential therapeutic target

Here are some possible treatments for CVD by lowing plasma TMAO levels.

4.1 Ginger

In 2019, Zouyan He et al[7] built a TMAO-exacerbated hypercholesterolemic mice model, they divided mice into five groups, each group had different levels of ginger extract (GE) and TMAO, after 12 weeks, they found GE could reduce the increase of plasma total cholesterol (TC) in mice fed with high cholesterol, and partially reversed the TMAO-induced reduction of total acid sterol in feces. That's to say, GE could reduce vascular inflammation caused by TMAO, thereby achieving cardiovascular protection.

A systematic review showed systolic blood pressure (BP) and diastolic BP were decreased by ginger dosage, this may be associated with an organic compound similar to salicylic acid in GE, which has a special effect on falling blood fat and arterial BP of body circulation, preventing myocardial infarction. However, CVD patients should not eat excessive ginger, because gingerol has a bad influence on the digestive organ.

4.2 Regulate intestinal flora

Dysbiosis occurs when the proportions of these bacteria change quantitatively or qualitatively, which may lead to increases in TMAO. Some bacteria are responsible for fermenting carnitine in food to produce TMAO, and these bacteria contain genes for enzymes involved in the synthesis of TMA. So changing the concentration of TMAO by regulating the abundance of intestinal flora may be a feasible approach. In 2019, a study applied spectroscopic low-absorption antibiotics in mice and then measured plasma TMAO levels, then they concluded: improving gut microbiome abundance can reverse the increased inflammation of blood vessels and arterial dysfunction associated with aging. But I don't recommend that people use antibiotics in large quantities for a long time because of possible adverse effects (dysbacteriosis, drug-resistant bacteria,

etc). Compared to antibiotics, probiotics can safely maintain the balance of intestinal flora, because it has been known that appropriate intake of probiotics can stimulate beneficial bacteria and inhibit harmful bacteria, thus regulating the balance of intestinal flora. By contrast, there was no reduction in TMAO levels during one month of probiotic supplements in males. The relationship between probiotics and TMAO cannot be generalized as different probiotics have different ways of acting on the gut.

4.3 Vitamin D

Vitamin D is a steroid derivative, which has been linked to immune system diseases, and gut microbiome also have influences on the immune system. Recently, more and more studies have shown that vitamin D may have a close relationship with the intestinal barrier. An in vitro test showed vitamin D inhibited the growth of some mycobacteria, so the bacteriostatic effect of vitamin D may be related to its immunomodulatory effect on intestinal microorganisms. However, bacteria may actually control the metabolism of vitamin D by synthesizing some related enzymes, such as CYP105. The mechanisms of how vitamin D affects intestinal flora stay unrevealed. In 2020, a secondary analysis suggested that the mechanism underlying the increased tendency for carnitine and TMAO with the vitamin supplements is changes in skeletal muscle. Studies have suggested that vitamin D may lead to high plasma TMAO levels, and then further lead to increased intestinal permeability. However, according to Obeid R et al research, vitamin D could bring down TMAO levels associated with homocysteine reduction.

5. Conclusion

In last few years, there is grown concert about the effects of diet and gut bacteria on CVD. L-carnitine, which is abundant in red meat, and TMAO, which is derived from its metabolic transformation through intestinal flora, have also sparked a lot of research. Based on articles published in recent years, I believe that TMAO may indeed increase the risk of CVD, and the metabolic pathway of choline conversion to TMAO may has many therapeutic targets for human intervention. The most promising approach is to suppress TMAO production by controlling the genes involved in the synthase. Of course, many researchers have tried dietary therapy, but the experimental results vary greatly in different ages, genders and regions, so we have not yet determined whether TMAO levels can be modulated by dietary control. Currently, we do not know the specific mechanism of how TMAO plays a role in CVD, I think the next research direction should be to fill this gap. In addition, influencing TMAO metabolism through the regulation of intestinal flora by probiotics is an idea worth exploring further.

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