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Review

Gut microbiota metabolism of L-carnitine and cardiovascular risk

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ABSTRACT

In recent years, a number of studies have alluded to the importance of the intestinal microflora in controlling whole-body metabolic homeostasis and organ physiology. In particular, it has been suggested that the hepatic production of trimethylamine-*N*-oxide (TMAO) from gut microbiota-derived trimethylamine (TMA) may enhance cardiovascular risk via promoting atherosclerotic lesion development. The source of TMA production via the gut microbiota appears to originate from 2 principle sources, either phosphatidylcholine/choline and/or L-carnitine. Therefore, it has been postulated that consumption of these dietary sources, which are often found in large quantities in red meats, may be critical factors promoting cardiovascular risk. In contrast, a number of studies demonstrate beneficial properties for L-carnitine consumption against metabolic diseases including skeletal muscle insulin resistance and ischemic heart disease. Furthermore, fish are a significant source of TMAO, but dietary fish consumption and fish oil supplementation may exhibit positive effects on cardiovascular health. In this mini-review we will discuss the discrepancies regarding L-carnitine supplementation and its possible negative effects on cardiovascular risk through potential increases in TMAO production, as well as its positive effects on metabolic health via increasing glucose metabolism in the muscle and heart.

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1. Introduction

Cardiovascular disease is a leading cause of death world wide, of which a significant portion can be attributed to ischemic heart disease, often as a result of underlying coronary artery disease due to atherosclerosis. Risk factors for atherosclerosis include dyslipidemia (i.e. elevated serum cholesterol, triglycerides, and low-density lipoproteins), hypertension, obesity, smoking, and diabetes [1,2]. Current therapies for atherosclerosis that target these risk factors, such as the first-line therapy statins (which inhibit 3-hydroxy-3-methyl-glutaryl-CoA reductase to reduce cholesterol production) are quite effective in preventing and treating this

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disease [3]. However, there remains a large number of patients that are refractory to statin therapy and other conventional therapies who will see their atherosclerotic disease worsen, and will ultimately die of other cardiovascular diseases such as myocardial infarction (MI) or stroke [4]. Therefore, there is a growing need to better understand the mechanisms contributing to the formation of the atherosclerotic plaque, and how to reverse its progression. In recent years, knowledge pertaining to the role of the intestinal microbiota as an external factor contributing to obesity and its associated co-morbidities has considerably grown [5].

Of interest, recent developments suggest that metabolism of dietary nutrients by the intestinal microbiota may contribute to atherosclerosis and subsequent cardiovascular disease in obese rodents and humans [6–8]. The aims of this mini-review are: (1) to highlight the role of the intestinal microbiota in atherosclerosis development, (2) to discuss the dependency of this effect on microbiota-derived trimethylamine-*N*-oxide (TMAO), and (3) to challenge the notion that enhanced L-carnitine metabolism in obesity may increase cardiovascular risk, due to L-carnitine acting as the major driver of TMAO production via the gut microbiota.

2. Gut microbiota-derived trimethylamine-*N*-oxide and cardiovascular risk

Trimethylamine (TMA) produced via the gut microbiota is oxidized with hydrogen peroxide via the enzymatic activity of hepatic flavin monooxygenase (FMO), resulting in the production of the organic compound, TMAO (Fig. 1). As such, consumption of compounds that can produce TMAO, such as phosphatidylcholine (PC) and L-carnitine, has the potential to result in elevated circulating TMAO levels [6,8]. TMAO is also commonly found in large amounts in saltwater fish and various members of the *Elasmobranchii* fish subclass (i.e. sharks and rays), and studies suggest that it is a proatherogenic compound that is positively associated with increased cardiovascular risk in both rodents and humans [6–8].

Support for a proatherogenic action of TMAO was first demonstrated by Wang et al., who demonstrated that consumption of a choline-enriched diet (1% in food wt/wt) for 16 weeks increased macrophage foam cell formation and atherosclerotic lesion area in C57BL/6J-*Apoe*$^{-/-}$ mice [8]. Illustrating the dependence of the gut microbiota for this effect, these effects were eliminated in both male and female C57BL/6J-*Apoe*$^{-/-}$ mice supplemented with antibiotics in the drinking water during choline diet-enrichment. Similarly, Koeth et al. demonstrated that consumption of an L-carnitine-enriched diet (1.3% in drinking water) for 15 weeks exacerbated atherosclerotic lesion area in C57BL/6J-*Apoe*$^{-/-}$ female mice [6]. Once again, these effects were prevented in female mice supplemented with antibiotics in the drinking water during L-carnitine diet-enrichment. Alluding to the clinical relevance of these findings, humans subjected to a dietary PC-choline challenge (consumption of 2 hard-boiled eggs with yolk containing approximately 500 mg total choline combined, plus a gelatin capsule containing 250 mg of deuterium-labeled PC) exhibited a significant increase in both urine and plasma levels of TMAO and radiolabeled-TMAO [7]. Consumption of broad-spectrum oral antibiotics for 1 week in these same participants resulted in an almost complete suppression of detectable TMAO and radiolabeled-TMAO during an identical PC-choline dietary challenge, which reverted back to normal during a third PC-choline dietary challenge following antibiotic withdrawal for at least a month [7]. In addition, a 3-year follow up of over 4000 patients undergoing coronary angiography examining the relationship between fasting plasma levels of TMAO and incident major cardiovascular events including MI and death, reported a significant positive correlation between the two variables [7].

The mechanisms by which TMAO promote atherosclerosis and increase cardiovascular risk are not completely understood, but it has been demonstrated that TMAO arising from both choline and L-carnitine diet supplementation in mice may inhibit reverse cholesterol transport (RCT) [6]. This reduction in RCT was attenuated in mice treated with antibiotics, highlighting the importance

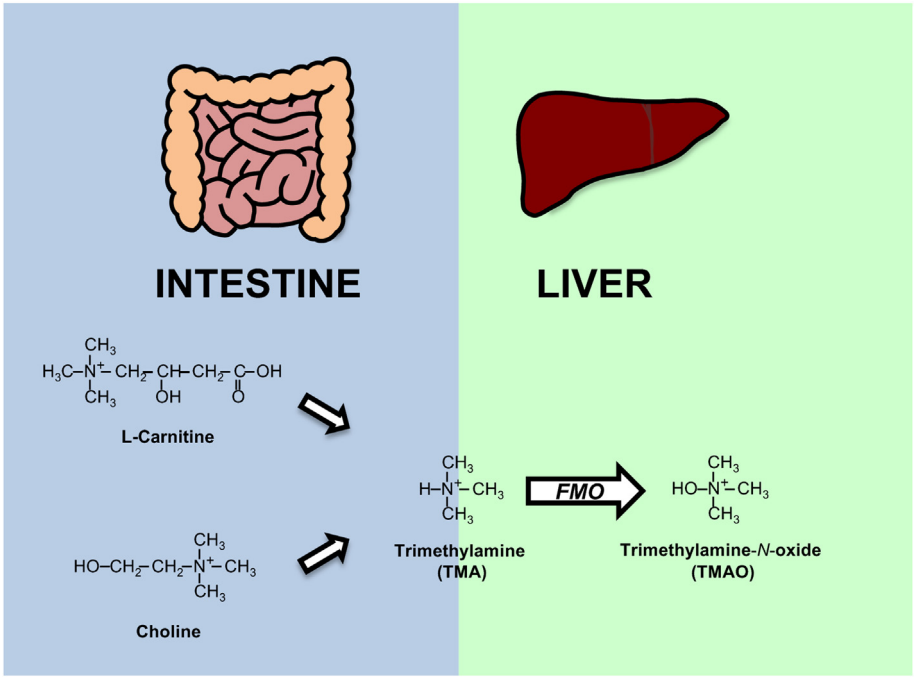

Fig. 1. Gut microbiota-dependent production of TMAO. The bacteria inhabiting the intestine are able to produce TMA from the TMA-containing compounds choline and L-carnitine, which are obtained in significant quantities from dietary red meats, eggs, and dairy products. This gut microbiota-derived TMA is subsequently converted into TMAO in the liver by the enzymatic activity of FMO. FMO – flavin monooxygenase, TMA – trimethylamine, TMAO – trimethylamine-*N*-oxide.