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Berberine treats atherosclerosis via a vitamine-like effect down-regulating Choline-TMA-TMAO production pathway in gut microbiota

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Abstract

Trimethylamine-*N*-oxide (TMAO) derived from the gut microbiota is an atherogenic metabolite. This study investigates whether or not berberine (BBR) could reduce TMAO production in the gut microbiota and treat atherosclerosis. Effects of BBR on TMAO production in the gut microbiota, as well as on plaque development in atherosclerosis were investigated in the culture of animal intestinal bacterial, HFD-fed animals and atherosclerotic patients, respectively. We found that oral BBR in animals lowers TMAO biosynthesis in intestine through interacting with the enzyme/co-enzyme of choline-trimethylamine lyase (CutC) and flavin-containing monooxygenase (FMO) in the gut microbiota. This action was performed by BBR's metabolite dihydroberberine (a reductive BBR by nitroreductase in the gut microbiota), via a vitamine-like effect down-regulating Choline-TMA-TMAO production pathway. Oral BBR decreased TMAO production in animal intestine, lowered blood TMAO and interrupted plaque formation in blood vessels in the HFD-fed hamsters. Moreover, 21 patients

with atherosclerosis exhibited the average decrease of plaque score by 3.2% after oral BBR (0.5 g, bid) for 4 months ($^*P < 0.05$, $n = 21$); whereas the plaque score in patients treated with rosuvastatin plus aspirin, or clopidogrel sulfate or ticagrelor (4 months, $n = 12$) increased by 1.9%. TMA and TMAO in patients decreased by 38 and 29% in faeces ($^*P < 0.05$; $^*P < 0.05$), and 37 and 35% in plasma ($^{***}P < 0.001$; $^*P < 0.05$), after 4 months on BBR. BBR might treat atherosclerotic plaque at least partially through decreasing TMAO in a mode of action similar to that of vitamins.

Subject terms: Drug discovery, Biotechnology

Introduction

Cardiovascular diseases (CVDs) have become the leading cause of mortality with a high rate of death.[1,2] Among the pathological changes of the diseases, atherosclerosis (AS) is often a common basis of CVDs and an intractable lesion with increased incidences over the years.[3,4] There are multiple risk factors and molecular mechanisms that contribute to the pathogenesis of AS,[5] such as high blood lipids or glucose, local or systemic inflammatory responses et al.[1,6] Recently, accumulating evidences revealed that the gut microbiota is an influential factor in the development and aggravation of AS.[7,8] For example, metabolites from gut microbiota (such as SCFAs) could play a vital role in down-regulating blood cholesterol or glucose[9,10] and inhibiting inflammation.[11] In fact, discovery of drugs that treat diseases through the gut microbiota is becoming attractive.[6,9,12,13]

Trimethylamine (TMA) is an intestinal bacteria-derived metabolite, generated through decomposition of dietary phosphatidylcholine/choline, or L-carnitine, or betaine[7,14–17] in ingested red meat or animal pluck.[18] Intestinal TMA absorbed into the blood is further transformed into its proatherogenic form, namely, trimethylamine-*N*-oxide (TMAO) by flavin monooxygenase family members, such as flavin monooxygenase 3 (FMO_3) in the liver.[19] Recent study has shown that TMAO is an independent predictor and promoter of AS, different from traditional risk factors.[14] In fact, TMAO aggravated AS through various mechanisms,[7] including enhanced effects on foam cell formation,[20] platelet hyper-reactivity and thrombosis risks,[17,21] direct activation of the inflammatory response[22,23] and interfering with the reverse transport of cholesterol.[24] Intervention studies focusing on TMAO production showed an obviously attenuated effect on AS in animals and human, suggesting the potential of this new target in the gut microbiota.[14,16] Thus, TMAO is the focused molecule of our study.

Berberine (BBR) is an active compound isolated from Chinese traditional medicine *Coptidis Rhizoma* (Fig. 1a),[25] and has been used to treat bacterial-caused diarrhoea as an over-the-counter (OTC) drug in China for decades. Since 2004, our group, as well as others, have identified BBR to be a safe and

effective medicine for hyperlipidaemia and type 2 diabetes in clinic,[26–28] with mechanisms and mode of action very different from the known drugs.[26,29] The reported mechanisms include the up-regulation of low-density lipoprotein receptor (LDLR)[26] and insulin receptor gene expression, activation of AMPK, inhibition of proprotein convertase subtilisin/kexin type 9 expression,[30] and others.[31] Although recent studies in animals have shown that BBR also exhibited inhibitory effect on plaque development in AS,[32,33] little is known about the mechanism. The oral bioavailability of BBR is probably about 1%,[34,35] suggesting the possible role of the gut microbiota in BBR's therapeutic effect against AS.[9,36–41]