Clinics and Research in Hepatology and Gastroenterology (2017) xxx, xxx–xxx

Available online at ScienceDirect www.sciencedirect.com

Elsevier Masson France EM|consulte www.em-consulte.com/en

MINI REVIEW

Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies

Yongbo Kang[a,b,*], **Yue Cai**[a,c]

[a] *Medical School, Kunming University of Science and Technology, Kunming 650500, Yunnan, China*
[b] *Genetics and Pharmacogenomics Laboratory, Kunming University of Science and Technology, Kunming 650500, Yunnan, China*
[c] *Pathogen biology Laboratory, Kunming University of Science and Technology, Kunming 650500, Yunnan, China*

KEYWORDS
Gut microbiota dysbiosis;
Metagenomics;
Hypertension;
Metabolic disorders;
Probiotic therapy

Summary Hypertension (HTN) has become a global public health concern and a major risk factor for cardiovascular, cerebrovascular, and kidney diseases. The complex interplay of genetic and environmental influences is important for the development of the disease. Accumulating evidence has illustrated the association of dysbiosis of gut microbiota with hypertension. Certain gut microbial strains may play either a pathogenic or a protective role in the development of hypertension. Oral probiotics can therefore represent a therapeutic approach for hypertension treatment. However, the relevant scientific work has only just begun, and the available data in this field remain limited. Fortunately, recent technological developments that permit identification of microbes and their products using culture-independent molecular detection techniques. In this review, we summarize the role of gut microbiota in hypertension progression, and probiotics in the treatment of hypertension.

Introduction

Hypertension (HTN) is a common disorder that affects a large heterogeneous patient population and which has major public health and economic implications. By 2025, the total number of hypertensive patients is expected to increase to 1.56 billion globally [1]. HTN is the leading cause of cardiovascular and renal diseases, including stroke, heart failure, coronary heart disease, and chronic kidney disease. HTN is estimated to affect more than one billion people worldwide. It accounts for 13% of all deaths, and seven million premature deaths per year [2]. Similar to other disease states, idiopathic HTN is called 'essential' or 'primary' when its exact cause and pathophysiology are unknown. Known, direct causes of HTN are identified in only 5–10% of all cases and are designated as 'secondary' owing to a precise underlying pathophysiological mechanism [3,4]. Although studies on genetic predisposition to HTN have implicated genes (e.g., *M235T*, *T174M*, *ATP2B1*, *GNB3*, NOS3) [5–8], the etiology of systemic inflammation still needs to be further discussed. Several studies have demonstrated potential

* Corresponding author. Medical faculty, Kunming University of Science and Technology, No. 727 South Jingming Rd., Chenggong District, 650500 Kunming, China.
E-mail addresses: y.kang@kmust.edu.cn, 657151276@qq.com (Y. Kang).

https://doi.org/10.1016/j.clinre.2017.09.006
2210-7401/

Please cite this article in press as: Kang Y, Cai Y. Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies. Clin Res Hepatol Gastroenterol (2017), https://doi.org/10.1016/j.clinre.2017.09.006

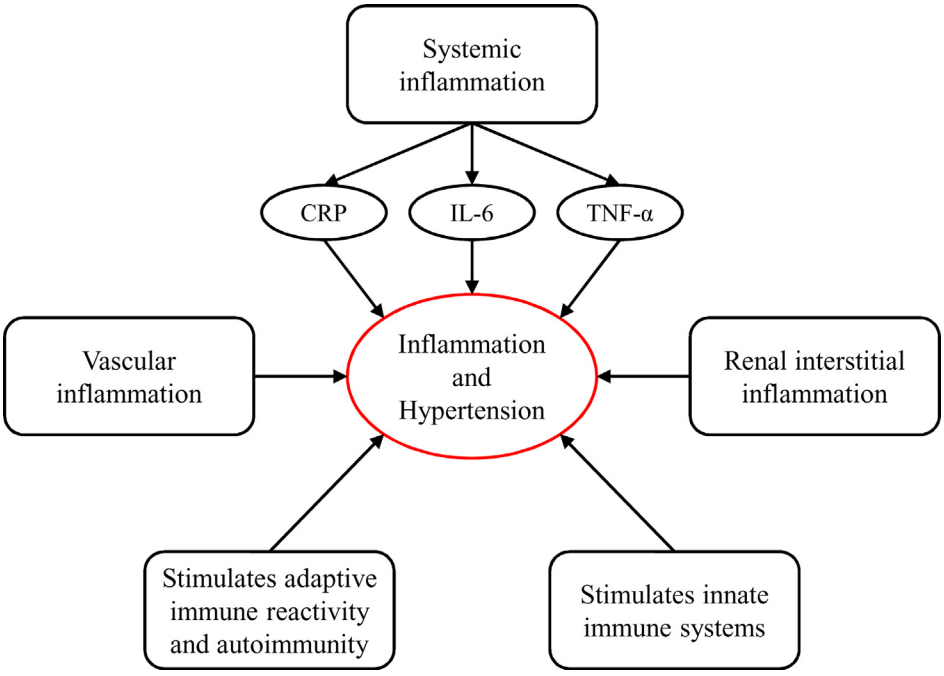

Figure 1 Potential association between inflammation and hypertension. CRP: C-reactive protein; IL-6: interleukin-6; TNF-α: tumor necrosis factor-α.

link between inflammation and HTN [9] (Fig. 1). There is a huge population of resident microbes in the intestine of an individual [10,11]. These organisms play a vital role in human health and simultaneously provide critical signals for the development of host immunity. Recent studies in animal models and human subjects have revealed that dysbiosis of the gut microbiota is associated with HTN progression [12—15]. Changes in the abundance of some gut microbial strains have been shown to inhibit or attenuate immune responses associated with chronic inflammation, and they may be biomarkers for HTN prevention and treatment. Though still a relatively nascent field of research, evidence to date suggest that the gut microbiome may represent fertile targets for prevention or management of HTN. In this review, we summarize recent literature to help further understand how the alteration of gut microbiota composition contributes to HTN. The therapeutic effect of probiotics in the treatment of HTN is also evaluated based on previous publications.

The role of gut microbiota in hypertension pathogenesis

Hypertension pathogenesis

HTN is the most common chronic disease characterized by a sustained systolic blood pressure (BP) value of $\geq$ 140 mmHg and a diastolic pressure of $\geq$ 90 mmHg (140/90) in young persons. Meanwhile, BP increases with age and hence only elderly people $\geq$ 60 years with BPs above 150/90 mmHg may require treatment [16]. HTN is the major cause of heart failure, stroke, chronic kidney disease and mortality worldwide. The pathogenesis of HTN is complex. Studies on genetic predisposition to HTN have implicated HTN-related genes such as *M235T*, *T174M*, BMPR2 and *GNB3* [5,17,18], and environmental factors have also been shown to contribute to disease pathogenesis. Changes in vascular structure and function are critical processes in the pathologies and include endothelial dysfunction, altered contractility, and vascular remodelling [19,20]. A number of pathways such as the fluid and electrolyte balance pathway, the renin-angiotensin system (RAS), the kinin-kallikrein system, the neutral endopeptidase system, and the endothelin-converting enzyme system are known to control human BP [21]. There are also other possible mechanisms (Fig. 2), i.e., that gut microbiota can influence the production of various hormones such as serotonin, dopamine, and norepinephrine which can affect BP. In addition, the metabolites of gut microbiota such as p-cresol sulfate, indoxyl sulfate, trimethylamine N-oxide (TMAO), and short chain fatty acids (SCFAs) can profoundly affect the cardiovascular system [13]. The intestinal bacteria have profound effects on the hosts' biology including the ability of the kidney to excrete sodium load and regulate blood pressure [22,23]. Previous study had found that chronic kidney disease patients have elevated plasma levels of TMAO [24,25]. This elevation in plasma TMAO levels maybe mainly due to gut microbial action. SCFA produced by the gut microbiota [26] influence blood pressure that is related to renal sensory nerves [27,28]. These SCFAs activate two orphan G protein-coupled receptors, GPR41 (also known as Free Fatty Acid Receptor 3), GPR43 (also known as Free Fatty Acid Receptor 2), and olfactory receptor 78 (Olfr78) that can regulate blood pressure. Chronic low-grade inflammation maybe lead to HTN [29]. Low-grade inflammation can be the result of gut microbial action [30]. Thus, intestinal microbiota appear to contribute to the development of HTN by inducing

Please cite this article in press as: Kang Y, Cai Y. Gut microbiota and hypertension: From pathogenesis to new therapeutic strategies. Clin Res Hepatol Gastroenterol (2017), https://doi.org/10.1016/j.clinre.2017.09.006