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COMMENT

Gut microbiota and hypertension

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Recently, attention has been focused on the potential importance of gut microbiota (GM) in human health. GM is considered to play a pivotal role in a variety of diseases, including hypertension (HT) and chronic kidney disease (CKD). This is because GM communicates with the endocrine, nervous, and immune systems to regulate host homeostasis, including blood pressure (BP) and renal function. CKD is commonly associated with HT and is accompanied by immune dysregulation, metabolic disorder, and sympathetic activation, which are all associated with gut dysbiosis [1]. Therefore, maintaining and recovering the homeostasis of the GM environment may be a possible therapeutic approach to treat CKD and HT.

This commentary is in response to the article by Onal et al., which reviews in detail the relationship between GM and cardiovascular disease in CKD [2]. Indeed, the production of uremic toxins in CKD may cause inflammation in various tissues and exacerbate cardiovascular disease. In this commentary, we would like to focus on how GM plays an important role in HT, because HT is an important, widespread cardiovascular disease.

Since Honour reported that BP was increased by altering rat GM with antibiotics in 1982, there is increased evidence on the relationship between GM and HT [3]. Antibiotics are likely to directly affect GM, so there are some articles on the effect of antibiotics on HT. Minocycline attenuates angiotensin II-induced HT and causes a shift in GM composition [4]. However, the influence seems to be different depending on the type of HT and the type of antibiotic. Galla et al. reported that neomycin, minocycline, and vancomycin increased systolic BP in Dahl salt-sensitive hypertensive rats. On the other hand, these three antibiotics reduced systolic BP in spontaneously hypertensive rats [5]. Therefore, depending on the type of animal model of HT and antibiotic, the effect may be different, and these studies need careful interpretation.

GM is important because the human body usually ingests nutrients that come from the intestine. Therefore, several key molecules have attracted attention that might play a role in the effect of GM on HT.

Excessive intake of salt is a risk for HT, and the sodium–proton exchanger subtype 3 (NHE3) plays an important role in the absorption of sodium and water, and pH regulation in the gut. Deletion of HNE3 altered the environment of gut microbiota and decreased the BP elevation induced by angiotensin II in mice [6, 7]. Therefore, GM may also be involved in the uptake of salt into the body.

Furthermore, it has recently been suggested that metabolites produced by GM may increase BP.

Short-chain fatty acids (SCFAs), including acetate, propionate, and butyrate, are only derived from the digestion of dietary fiber by GM and can be absorbed into the blood stream of the host. SCFAs can stimulate the regulatory pathways associated with G-protein-coupled receptors (GPCRs), including Gpr41 to increase sympathetic nerve activity, and Olfr78 to increase renin secretion. This increased sympathetic activity and renin secretion elevate BP and can be counteracted through Gpr 43 and Gpr109a to induce vasodilation [8].

If intestinal homeostasis fails, gut dysbiosis can produce proinflammatory cytokines and oxidative stress with an increase in free radicals, which can oxidize low-density-lipoprotein (LDL). Especially, lipopolysaccharide (LPS) is a cell wall component of Gram-negative bacteria that acts as pathogen-associated molecular patterns through toll-like receptor 4 signaling that increases the production of proinflammatory cytokines [9]. Oxidized LDL (oxLDL) is considered to be the cause of atherosclerosis, and oxLDL inhibits production of nitric oxide (NO), which can relax vasoconstriction and reduce BP. Higher levels of oxLDL

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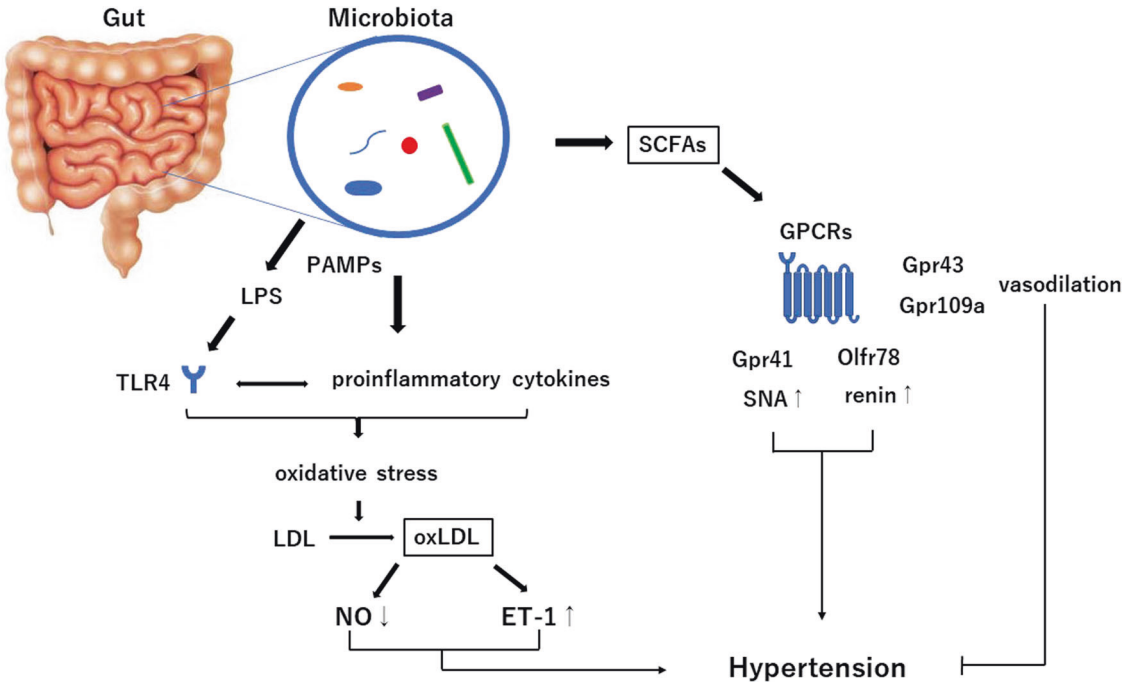

Fig. 1 Gut microbiota and possible mechanisms for hypertension. PAMPs pathogen-associated molecular patterns, LPS lipopolysaccharide, TLR4 toll-like receptor 4, LDL low-density-lipoprotein, oxLDL oxidized low-density-lipoprotein, NO nitric oxide, ET-1 endothelin-1, SCFAs short-chain fatty acids, GPCRs G-protein-coupled receptors, SNA sympathetic nerve activity

lead to increased BP with decreases in NO and increases in endothelin-1 [10]. These mechanisms have a great influence not only on regulation of BP, but also on the progression of atherosclerosis. These mechanisms are shown in the Figure.

Although there is much evidence on the effect of GM on BP in animal experiments, unfortunately, there is not much verification of this evidence in humans. In human studies, a meta-analysis suggests that probiotic consumption significantly changed systolic BP by −3.56 mm Hg and diastolic BP by −2.38 mm Hg compared with control [11]. Moreover, a greater reduction in BP was recognized with multiple species of probiotics (Fig. 1). Individuals with baseline BP ≥ 130/85 mm Hg showed a more significant reduction in diastolic BP. Intervention for < 8 weeks did not result in a significant reduction in systolic or diastolic BP. Based on this meta-analysis, intervention with multiple species of probiotics may have a modest effect on BP in hypertensive patients, although the effect may not be as strong as the effect of antihypertensive drugs.

On the other hand, in a randomized double-blind placebo-control trial using GM manipulation by antibiotics (7-day administration of amoxicillin, vancomycin, or placebo) to evaluate host metabolism in 57 obese prediabetic men, vancomycin but not amoxicillin, decreased bacterial diversity and reduced firmicutes involved in SCFA and bile acid metabolism, concomitant with altered plasma and/or fecal metabolite concentrations. Adipose tissue gene expression in oxidative pathways was upregulated by antibiotics, whereas immune-related pathways were downregulated by vancomycin. Finally, the use of antibiotics did not change energy/substrate metabolism, including tissue-specific insulin sensitivity, postprandial hormones and metabolites, systemic inflammation, gut permeability, and the size of adipocytes. Moreover, changes in energy harvest, adipocyte size, and whole-body insulin sensitivity were not recognized at 8 weeks of follow-up, despite a considerable modification of microbial composition. This study indicates that antibiotic treatment has no clinically relevant influence on metabolic health in obese humans [12]. Looking back on this research, the duration of administration may have been too short. Based on the previous meta-analysis, intervention for more than 8 weeks may be necessary to alter GM and obtain physiologically effective outcomes. However, it is still doubtful whether it will be reasonable for medical practitioners to prescribe antibiotics for more than 2 months.

Although GM is expected to be a therapeutic target for cardiovascular disease in the near future, the evidence at the present time is not sufficient, and there are still many unanswered questions. It is desirable to develop a gentle method to change the GM, such as probiotics and antibiotics, which can be used for a long time.

Compliance with ethical standards

Conflict of interest JO belongs to the endowed department of Fukuda Denshi Co, Ltd. KN received remuneration including lecture fees from

AstraZeneca, Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Pfizer Inc, MSD K.K., Daiichi Sankyo Company, Ltd, Kowa Pharmaceutical Co, Ltd, Takeda Pharmaceutical Co, Ltd, Novartis Pharmaceuticals Japan, Mitsubishi Tanabe Pharma Corporation, and Dainippon Sumitomo Pharma Co, Ltd. KN also received scholarship funds or donations granted by Astellas Pharma Inc, Nippon Boehringer Ingelheim Co, Ltd, Daiichi Sankyo Company, Ltd, Takeda Pharmaceutical Co, Ltd, Mitsubishi Tanabe Pharma Corporation, and MSD K.K.

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