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Medical Bulletin

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ASSOCIATION OF GUT MICROBIOTA AND HYPERTENSION

The human gastrointestinal tract harbors more microorganisms than the total number of human cells. These microorganisms contain around 100 times the number of genes than that found in the human genome, making them the “human second genome” that affects overall host health. Collectively, these microorganisms are known as the gut microbiota, which is composed of fungi, viruses, archaea, protists, and dominant bacteria. Under normal conditions, the intestinal microbiota contributes to the host homeostasis through several aspects.

1) It takes part in the nutrient absorption and the energy metabolism of human body.
2) It regulates host immune responses.
3) It protects the intestinal epithelial barrier function.

Maintaining the variety and balance of gut microbiota is the key point for promoting human health. The gut microbiota is primarily composed of Bacteroidetes, Firmicutes, Actinobacteria, Proteobacteria, Verrucomicrobia, and Fusobacteria. Alteration in the diversity or structure of gut microbiota known as ***dysbiosis*** is associated with autoimmune/allergic, metabolic, gastrointestinal and cardiovascular diseases.

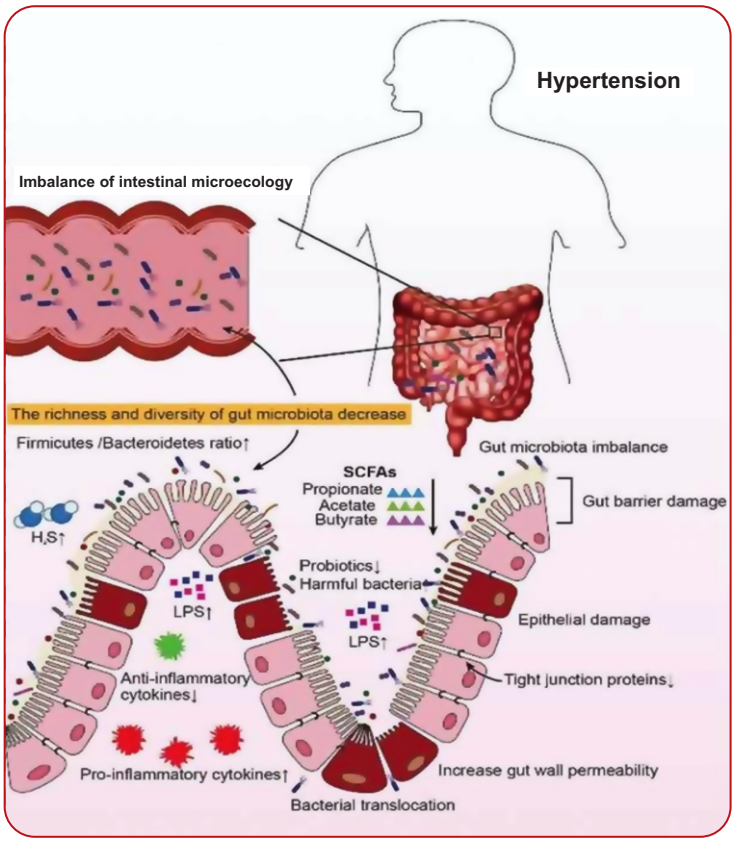
Besides the known pathogenesis of hypertension, recent research have indicated that the human intestinal microbiota plays an important role in the occurrence and development of ***hypertension***. Existing evidence has proven that gut barrier function, gut microbiota structure and gut microbial metabolites are key factors involved in the occurrence and development of hypertension.

✤ Gut microbiome barrier function in the regulation of blood pressure

- When the gut barrier function is normal, the intestinal permeability is low, which can effectively inhibit the leakage of intestinal pathogens, enteroendotoxins and other substances into the body and reduce the inflammatory damage to intestinal blood vessels, thereby maintaining normal blood pressure (BP).
- ***Gut barrier dysfunction plays a role in the pathogenesis of hypertension.***
- The dysfunction not only causes dysbiosis of gut microbiota, but also leads to an increase in intestinal permeability. This results in translocation of bacteria and toxic products into the blood circulation and causes systemic inflammation. These further lead to endothelial cell dysfunction and vascular sclerosis, causing or aggravating hypertension.

✤ Gut microbiota structure and the regulation of blood pressure

- The normal composition of gut microbiota is essential to maintain the health of the body. Increased F/B ratio (abundances of Firmicutes



over Bacteroidetes) is often used as an indicator of gut microbial dysbiosis. The occurrence and progress of hypertension is closely related to this increased ratio with studies confirming the same.

- High salt intake was found to change the composition of gut microbiota and their circulating metabolites, increase the F/B ratio & promote inflammatory responses (increased CD4+, IL-17A+, and Th17 cells in the intestinal immune system).
- Increase in these inflammatory cytokines promote the reabsorption of sodium ions by the renal tubules which leads to the retention of water and sodium in the body, causing hypertension.
- Pre-clinical studies have found that Losartan, an effective antihypertensive agent restored the F/B ratio and improved dysbiosis. In addition, Losartan improved intestinal barrier integrity and reduced sympathetic drive. Thus, the protection of blood vessels and reduction in BP may be attributed to Losartan-induced changes in gut microbiota.

✤ Gut microbial metabolites and the regulation of blood pressure

The gut microbiota metabolites such as trimethylamine-N-oxide (TMAO), short-chain fatty acids (SCFAs), hydrogen sulfide (H2S), bile acids (BAs) and lipopolysaccharide (LPS) have diverse effects on BP regulation.

- SCFAs (mainly acetate, propionate & butyrate) derived from dietary fiber fermentation, can be absorbed from the intestine via the gut epithelium, enter the circulation and bind to G-protein-coupled receptors (GPCRs). GPCRs are proteins that are located in the cell membrane. They regulate BP by modulating the dynamic balance of vasoconstriction and relaxation. SCFAs interacts with at least four GPCRs to regulate BP – GPR41, GPR43, GPR109 and olfactory receptor 78 (Olfr78).
  i. By binding to GPR41 in vascular endothelial cells, SCFAs can cause vasodilation, which lowers BP. SCFAs can also relax mesenteric arteries through the GPR41/ GPR43 pathway, attenuating hypertension. It can protect podocytes on the glomerular basement membrane by acting through GPR109A, improving proteinuria, reducing glomerulosclerosis and tissue inflammation and ultimately lowering BP.
  ii. On the contrary, activation of Olfr78 may increase BP through the response of juxtaglomerular cells to SCFAs which promotes cyclic adenosine monophosphate production and increases renin release.
- BAs exhibit antihypertensive effects due to their capability to lower succinate, a proven pro-hypertensive metabolite.
- H2S participates in physiological processes like smooth muscle relaxation, oxidative regulation & inflammation. It is an endogenous vasoactive factor that causes concentration dependent vasodilation. Studies have shown that increased H2S in the gut can reduce BP and vice versa. In addition, it can lower BP by reducing the synthesis and release of renin. It may also lower

BP by dilating peripheral blood vessels and lowering heart rate.

- Trimethylamine (TMA) is a gut microbiota-derived metabolite produced from the metabolism of food components mainly dietary choline, betaine and carnitine. Oxidation of TMA in the host liver generates TMAO. Alterations in microbiota composition are responsible for increased TMAO levels in response to the diet. Studies have showed that high levels of TMAO is associated with significantly higher incidence of hypertension. It increases BP in an indirect manner by enhancing the pro-hypertensive effect of Angiotensin II. Other studies have shown that TMAO can increase BP by inducing vascular endothelial dysfunction, achieved by promoting oxidative stress and production of inflammatory mediators in vascular endothelial cells.
- Gut microbiota disturbance can cause increased secretion and release of intestinal LPS into the blood circulation. This promotes its entry in the circulation to trigger inflammatory response aggravating hypertension.

Maintaining and recovering the homeostasis of the gut microbiota environment through proper diet, exercise and appropriate use of antihypertensive medication based on individual patient characteristics may be a possible therapeutic approach to treating hypertension.

Source: *Gao K, et al. Gut Microbes. 2024; 16 (1): 2356278, Yang Z, et al. Clin. Exp. Hypertens. 2023; 45(1): 2195135, Yan D, et al. Animal Model Exp Med. 2022; 5(6): 513–531.*

IMPACT OF VITAMIN B12 DEFICIENCY ON ISCHEMIC STROKE

Cerebral ischemia/reperfusion injury is a complicated pathological process accompanied by inflammation, oxidative stress, neuronal apoptosis, autophagy and excitotoxicity. It is common in ***ischemic stroke*** and can aggravate neurological damage after cerebral ischemia.

Ischemic stroke, is characterized by high morbidity, mortality, disability and recurrence rates. Many factors contribute to stroke risk and outcomes, making it highly multifactorial. Nutrition is a modifiable risk factor for stroke. Vitamin B12 deficiency is a well-established risk factor for stroke and worse clinical outcomes. Approximately 20% of older adults (>60 years old) have vitamin B12 deficiency, making it of high concern to this population because with aging, the transport mechanisms of getting vitamin B12 across the blood-brain barrier become damaged.

Neurons in the ischemic penumbra suffer transient reversible injury, which allows neurons to survive for a short period. This salvageable tissue is the target for neuroprotective therapy. During the reversible injury phase, inflammation and oxidative stress play a crucial role in its pathogenesis.

Methylcobalamin (MeCbl) is an endogenous form of vitamin B12. MeCbl can promote axonal transport, axonal regeneration, myelin formation and repair damaged nerve tissue. It has been shown to exhibit anti-inflammatory, antioxidant and anti-apoptotic activities in a variety of diseases.

✤ Role of Vitamin B12 in Stroke

I. Vitamin B12 plays several roles within the cell and is involved in the methylation of homocysteine and thereby generation of S-adenosylmethionine, a global methyl donor. Increased levels of plasma homocysteine (> 10 µM) or methylmalonic acid (> 210 nM) can be helpful in determining whether a patient has a deficiency in vitamin B12.

- Increased levels of homocysteine lead to reduced levels of nitric oxide bioavailability, leading to changes in endothelial mediated dilation causing vascular damage due to the production of free radicals, as well as lipid peroxidation. Since, Vitamin B12 metabolizes homocysteine, increasing its level can be beneficial for patients with elevated levels of homocysteine in terms of reducing stroke risk.

II. Additionally, Vitamin B12 plays an essential role in mitochondrial energy production and cellular function. Mitochondria is a major contributor to the development of apoptotic and necrotic cell death after ischemic stroke. A pre-clinical study have found that mitochondria metabolite changes takes place in the brain tissue after ischemic stroke with vitamin B12 deficiency state.

III. Recent data indicates that vitamin B12 plays a crucial role as an antioxidant, and decreased levels lead to increased oxidation. The increased levels of oxidation lead to the activation of nuclear factor-erythroid factor 2-related factor (Nrf-2), an important transcription factor involved in the cellular response to oxidative stress. Ischemic stroke also results in oxidative stress and increased levels of Nrf-2. Pre-clinical studies have shown supplementation with vitamin B12 results in increased levels of Nrf-2 and superoxide dismutase 2 (SOD2).

- Another study has described that vitamin B12 can act as a scavenger for reactive oxygen species (ROS) after renal ischemia and reperfusion, as well as reduce inflammation. So, possibly through its antioxidant role, dietary supplementation of vitamin B12 after stroke has been shown to provide benefits in preclinical models of stroke as well as in clinical studies.

IV. Extracellular signal-regulated protein kinases 1 and 2 (ERK1/2), an important subfamily of mitogen-activated protein kinases is essential for a wide range of cell activities, including cell apoptosis and survival. ERK1/2 plays a critical role in triggering neuroprotective effects in stroke and neurodegenerative disease by regulating the anti-apoptotic, anti-inflammatory and autophagy processes. One study demonstrated that activation of the ERK1/2 axis correlated positively with surviving neurons in models with neuronal injury and cerebral ischemia. MeCbl has also been shown to promote proliferation and inhibit apoptosis in nerve and muscle cells by activating the ERK1/2 signalling pathway, thereby supporting its neuroprotective role in stroke.

In a study of 725 stroke cases (455 ischemic, 125 haemorrhagic and 145 unknown incidents), increased dietary intake of vitamin B12 was significantly associated with a decreased risk of ischemic stroke in men aged 40–75 years.

Vitamin B12 supplementation may thus reduce stroke incidence, delay progression and improve stroke prognosis by acting as a neuroprotective agent against cerebral ischemia.

Source: *Jadavji NM, et al. Neurobiol. Dis. 2024; 103: 89-100, Li Y, et al. Int. Immunopharmacol. 2021; 99: 108040, Poole J, et al. Nutrients. 2022, 14(14), 2960, Yahn GB, et al. Neural Regen Res. 2021; 16(3): 470-474.*

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