Short-chain fatty acids in blood pressure, friend or foe

Xiao-Feng Chen1,2, Si-Chong Ren3, Guo Tang2, Chuan Wu1, Xiangqi Chen1, Xiao-Qiang Tang1

1Key Laboratory of Birth Defects and Related Diseases of Women and Children of Ministry of Education, State Key Laboratory of Biotherapy, West China Second University Hospital, Sichuan University, Chengdu, Sichuan 610041, China;
2Department of Biochemistry and Molecular Biology, Basic Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, China;
3Department of Nephrology, The First Affiliated Hospital of Chengdu Medical College, Chengdu, Sichuan 610500, China.

To the Editor: Gut microbiota, the trillions of microbes living in the human and rodent gut, play a pivotal role in cardiovascular diseases, including hypertension and atherosclerosis. One of the crucial mechanisms underlying gut microbiota functions in cardiovascular diseases is the microbiota-derived metabolites such as short-chain fatty acids (SCFAs). And emerging evidence demonstrated gut microbiota-derived metabolites — SCFAs maintained stable blood pressure.11 However, there is no large cohort study on the correlation of SCFAs with hypertension.

Recently, the HEalthy Life In an Urban Setting study conducted by Verhaar et al2 enrolled 4672 participants and reported the correlation of gut microbiota and SCFAs with blood pressure. This timely large cohort study strongly consolidated the potential participation of gut microbiota and microbiota-derived metabolites – SCFAs in blood pressure regulation. Based on this study, fecal microbiota composition explained 4.4% of the total systolic blood pressure (SBP) variance. Best predictors for SBP included SCFA-producing microbiota. A higher abundance of these SCFA-producing microbiota predicted lower SBP, whereas higher fecal SCFA levels were observed in participants with higher SBP. This phenomenon leads to the hypothesis that fecal SCFAs are not the direct connector between gut microbiota and blood pressure regulation. It would be interesting to test the predictive value of circulating SCFAs since the absorption/transportation of SCFAs and expression of SCFA receptors may be variable factors.11 Besides, some other gut-derived metabolites, for example, trimethylamine N-oxide, are also associated with an increased risk of hypertension.5

Gut microbiota ferments indigestible dietary fiber to generate SCFAs, mainly including acetate, propionate, and butyrate. Among them, acetate is the most abundant.4 Previous studies have shown a diet rich in fiber could change the composition of gut microbiota and increase the concentration of acetate-producing bacteria, ultimately attenuating gut dysbiosis and decreasing blood pressure. Similarly, direct supplementation with acetate would lower blood pressure,3 which means gut microbiota-derived acetate exerts a protective role in blood pressure regulation. And the moderate propionate fermented by gut bacteria also significantly attenuated hypertension in mice induced by angiotensin II through maintaining regulatory T cell-dependent immune homeostasis.6 Meanwhile, butyrate could inhibit angiotensin II-treated hypertension via suppression of renal (pro)renin receptor-mediated intrarenal renin-angiotensin system.7 Collectively, these researches demonstrated gut microbiota-derived metabolites – SCFA lowers blood pressure in rodents [Figure 1].

In this clinical study, the different correlations of SCFAs and SCFA-producing microbiota with blood pressure revealed the complex and multiple roles of microbiota and their metabolites in the cardiovascular system. An in-depth analysis of individual microbe, the metabolite, and the corresponding receptors (eg, G protein-coupled receptor 41 [GPR41], GPR42, GPR43, GPR91, GPR109A, GPR164, and olfactory receptor 78) would help understand their roles and mechanism in regulating blood pressure.1,4,11 Besides, our current study highlighted SCFAs such as crotonate was implicated in regulating histone crotonylation (crotonylated lysine 18 of histone H3 [H3K18cr] and lysine 12 of histone H2B [H2BK12cr]) and pathological cardiac hypertrophy.8 Further studies are also needed to verify if SCFAs (eg, acetate and propionate) prevent the development of hypertension via an epigenetic mechanism.

To conclude, gut microbiota and the most abundant SCFAs such as acetate, propionate, and butyrate from the
Fermentation of gut microbiota play an essential role in controlling blood pressure. Therefore, targeting the gut microbiota or dietary augmentation of the main SCFAs, such as acetate, propionate, and butyrate, could be novel antihypertensive therapies. Further studies are still needed to explore the potential of SCFAs for treating blood pressure and the underlying mechanisms.

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**Conflicts of interest**

None.

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