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

Xiao-Feng Chen[1,2], Si-Chong Ren[3], Guo Tang[2], Chuan Wu[1], Xiangqi Chen[1], Xiao-Qiang Tang[1]

[1]Key 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;
[2]Department of Biochemistry and Molecular Biology, Basic Medical College, Chengdu University of Traditional Chinese Medicine, Chengdu, Sichuan 611137, China;
[3]Department 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.[1] 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 al*[2] 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.[1] Besides, some other gut-derived metabolites, for example, trimethylamine N-oxide, are also associated with an increased risk of hypertension.[3]

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,[5] 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] 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

Access this article online

Quick Response Code:

Website: www.cmj.org

DOI: 10.1097/CM9.0000000000001578

Xiao-Feng Chen and Si-Chong Ren contributed equally to this article.

Correspondence to: Xiao-Qiang Tang, Key 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
E-Mail: tangxiaoqiang@scu.edu.cn; txiaoqiang@yeah.net

Chinese Medical Journal 2021;134(19)
Received: 14-01-2021 **Edited by:** Ning-Ning Wang

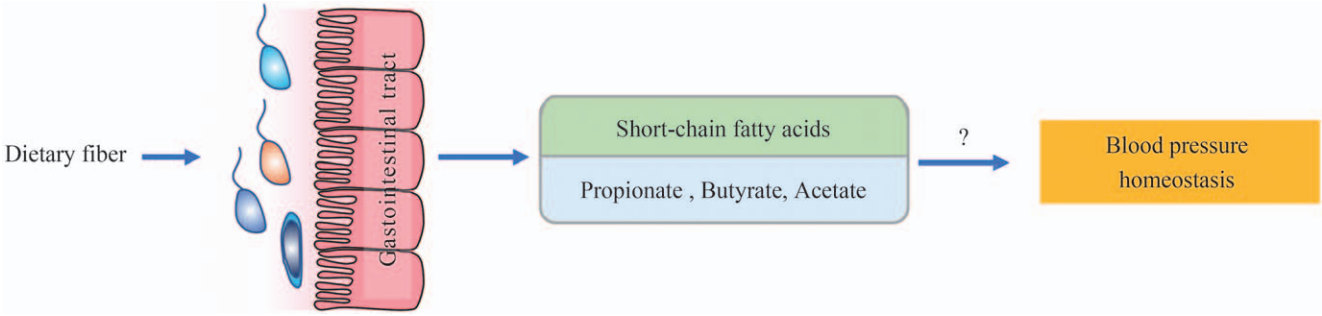

Figure 1: Effect of gut microbiota-derived SCFAs on blood pressure. Dietary fiber could change the composition of gut microbiota, further influence the generation of SCFAs fermented by gut bacteria to regulate blood pressure. However, the detailed mechanisms by which SCFAs regulate blood pressure remain to explore. SCFAs: Short-chain fatty acids.

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.

Funding

This work was supported by grants from the National Natural Science Foundation of China (No. 81970426, 81800273, and 82004097), the Young Elite Scientists Sponsorship Program of China Association for Science and Technology (No. 2018QNRC001), the Scientific and Technological Innovation Talents Program of Sichuan Province (No. 2020JDRC0017), and the China Postdoctoral Science Foundation (No. 2020M673163).

Conflicts of interest

None.

References

1. Chen XF, Chen X, Tang X. Short-chain fatty acid, acylation and cardiovascular diseases. Clin Sci (Lond) 2020;134:657–676. doi: 10.1042/CS20200128.
2. Verhaar BJH, Collard D, Prodan A, Levels JHM, Zwinderman AH, Bäckhed F, *et al*. Associations between gut microbiota, faecal short-chain fatty acids, and blood pressure across ethnic groups: the HELIUS study. Eur Heart J 2020;41:4259–4267. doi: 10.1093/eurheartj/ehaa704.
3. Ge X, Zheng L, Zhuang R, Yu P, Xu Z, Liu G, *et al*. The gut microbial metabolite trimethylamine N-oxide and hypertension risk: a systematic review and dose-response meta-analysis. Adv Nutr 2019;11:66–76. doi: 10.1093/advances/nmz064.
4. Kimura I, Ichimura A, Ohue-Kitano R, Igarashi M. Free fatty acid receptors in health and disease. Physiol Rev 2020;100:171–210. doi: 10.1152/physrev.00041.2018.
5. Marques FZ, Nelson E, Chu PY, Horlock D, Fiedler A, Ziemann M, *et al*. High-fiber diet and acetate supplementation change the gut microbiota and prevent the development of hypertension and heart failure in hypertensive mice. Circulation 2017;135:964–977. doi: 10.1161/CIRCULATIONAHA.116.024545.
6. Bartolomaeus H, Balogh A, Yakoub M, Homann S, Marko L, Hoges S, *et al*. Short-chain fatty acid propionate protects from hypertensive cardiovascular damage. Circulation 2019;139:1407–1421. doi: 10.1161/CIRCULATIONAHA.118.036652.
7. Wang L, Zhu Q, Lu A, Liu X, Zhang L, Xu C, *et al*. Sodium butyrate suppresses angiotensin II-induced hypertension by inhibition of renal (pro)renin receptor and intrarenal renin-angiotensin system. J Hypertens 2017;35:1899–1908. doi: 10.1097/HJH.0000000000001378.
8. Tang X, Chen XF, Sun X, Xu P, Zhao X, Tong Y, *et al*. Short-chain enoyl-CoA hydratase mediates histone crotonylation and contributes to cardiac homeostasis. Circulation 2021;143:1066–1069. doi: 10.1161/CIRCULATIONAHA.120.049438.

How to cite this article: Chen XF, Ren SC, Tang G, Wu C, Chen X, Tang XQ. Short-chain fatty acids in blood pressure, friend or foe. Chin Med J 2021;134:2393–2394. doi: 10.1097/CM9.0000000000001578