HOSTED BY
ELSEVIER
Available online at www.sciencedirect.com
ScienceDirect
Journal of Sport and Health Science

Commentary

Kidney betaine: A potential broad spectrum exercise mimetic against aging

Hongyun Wang [a,†], Xiaoying Yang [a,†], Chi Jin [a], T Scott Bowen [b,*], Junjie Xiao [a,*]

[a] *Cardiac Regeneration and Ageing Laboratory, Institute of Cardiovascular Sciences, Shanghai Engineering Research Center of Organ Repair, Joint International Research Laboratory of Biomaterials and Biotechnology in Organ Repair (Ministry of Education), School of Life Science, Shanghai University, Shanghai 200444, China*

[b] *School of Biomedical Sciences, University of Leeds, Leeds LS2 9JT, UK*

Received 8 July 2025; revised 28 August 2025; accepted 18 September 2025
Available online 9 October 2025

Physical activity, moderate aerobic or resistance exercise are well established to offer health benefits and promote healthy aging and longevity.[1] In contrast, lack of exercise contributes to adverse events, especially in some patients with organ failure.[2] Therefore, "exercise pills" and "exercise mimetics" have attracted growing interest because of their potential to induce exercise-related health effects despite physical exercise not being performed.[3] Robust studies over the past decade have identified many natural biomacromolecules, such as peptide, non-coding Ribonucleic Acid (RNAs) , and lipids, that are induced by exercise.[4–6] These molecules trigger physiological adaptations, including promotion of cardiomyocyte proliferation, anti-apoptotic capacity, and healthy tissue growth.[7] However, identifying or designing an exercise pill that mimics the extensive benefits of exercise is still challenging. Overall, exercise can induce several factors from sources such as brain, fat, plasma, and liver that perform beneficial effects. Notably, among these factors, our understanding of the myokine expression in response to exercise remains incomplete.[8]

In 2008, scientists identified that Acadesine (AICAR), an Adenosine 5'-monophosphate (AMP)-activated protein kinase (AMPK) agonist, promoted skeletal muscle reprogramming toward increased oxidative phenotype and exercise endurance in adult mice.[9] This study confirmed the effect of a compound that mimicked the benefits of exercise on skeletal muscle and highlighted a promising drug to increase endurance without the requirement for exercise, thus opening a new window for inducing exercise-like effects in the sedentary condition. However, a debate has arisen because recent exercise-mimetic compounds (e.g., AICAR, GW501516) primarily target muscles and therefore do not faithfully replicate the broad systematic effects of whole-body exercise. Therefore, whether exercise mimetics can substitute physical activity remains an open question.[10,11] Moreover, the clinical safety and potential adverse effects of such exercise mimetics remain controversial.[12] Balancing therapeutic promise against adverse effects will require further investigation.[9]

A recent study by Geng et al.[13] entitled "*Systematic profiling reveals betaine as an exercise mimetic for geroprotection*" was published in *Cell*. The systematic profiling analysis revealed that betaine, a natural metabolite induced by repeated exercise, displays extensive protective effects in aged mice. Researchers designed and conducted a muti-omics analysis and comprehensive verification showing that a renal synthesized exercise mimetic, betaine, exerts multi-organ geroprotective effects in aged mice. Supplementation with a physiological concentration of betaine provided systemic geroprotection across organs via inhibition of TANK-binding kinase 1 (TBK1), with reduced inflammation and senescence (Fig. 1). With growing drug development and global aging, exercise mimetics are attracting widespread attention as a treatment for age-related metabolic dysfunction and oxidative stress, and the findings by Geng et al.[13] further support their potential to promote healthy aging.

Betaine, a natural metabolite that exists extensively in plants and mammals, can be endogenously synthesized in the liver and kidney. The physiological role of betaine has been widely studied in different organs, a role which includes its anti-cancer capacity, hepatoprotection, cardioprotection, neural benefits, and nephroprotective effects.[14] These benefits are thought to be related to betaine's potential anti-oxidative stress and anti-inflammatory properties.[15] In addition, the diuretic potential of betaine is attractive for treating heart failure, a chronic disease characterized by excessive edema and exercise intolerance. Clinically, increased serum betaine

Peer review under responsibility of Shanghai University of Sport.
* Corresponding authors.
E-mail addresses: T.S.Bowen@leeds.ac.uk (T.S. Bowen), junjiexiao@shu.edu.cn (J. Xiao).
† These two authors contributed equally to this work.

https://doi.org/10.1016/j.jshs.2025.101092
Cite this article: Wang H, Yang X, Jin C, Bowen TS, Xiao J. Kidney betaine: A potential broad spectrum exercise mimetic against aging. *J Sport Health Sci* 2026;15:101092.

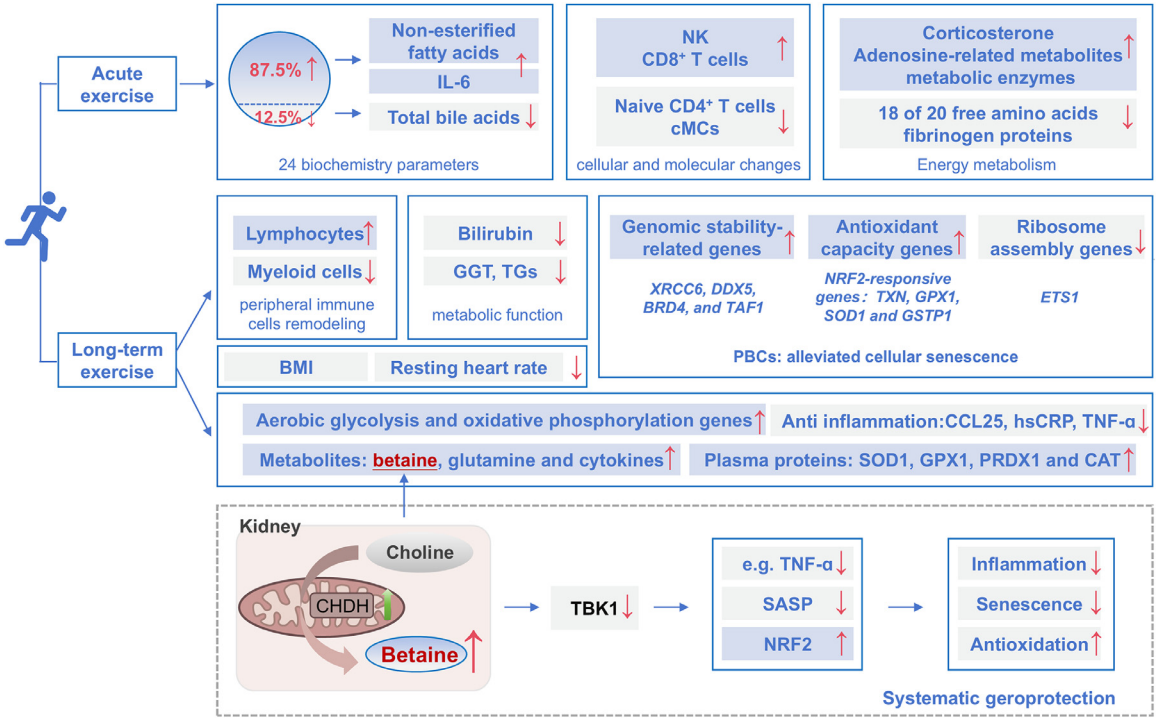

Fig. 1. Kidney betaine induced by long-term exercise exerts geroprotection. BMI = Body mass index; BRD4 = Bromodomain Containing Protein 4; CAT = Catalase; CCL25 = C-C Motif Chemokine Ligand 25; CHDH = Choline Dehydrogenase; cMCs = Circulating Mast Cells; DDX5 = DEAD-Box Helicase 5; ETS1 = ETS Proto-Oncogene 1, Transcription Factor; GGT = Gamma-Glutamyl Transferase; GPX1 = Glutathione Peroxidase 1; GSTP1 = Glutathione S-Transferase Pi 1; hsCRP = high-sensitivity C-Reactive Protein; IL-6 = Interleukin-6; NK = Natural Killer Cells; NRF2 = Nuclear factor erythroid 2-related factor 2; PBCs = Peripheral blood cells; PRDX1 = Peroxiredoxin 1; SASP = Senescence-Associated Secretory Phenotype; SOD1 = Superoxide Dismutase 1; TAF1 = TATA-Box Binding Protein Associated Factor 1; TBK1 = TANK-Binding Kinase 1; TGs = Triglycerides; TNF-α = Tumor Necrosis Factor Alpha; TXN = Thioredoxin; XRCC6 = X-Ray Repair Cross Complementing 6.

has been observed in heart failure patients, and there may be a link between betaine, other metabolites, and disease severity.[14,16]

Interestingly, the study by Geng et al.[13] revealed that exercise induces the most striking changes in gene expression in the kidney, followed by other tissues such as skeletal muscle and the liver. This finding further expands our knowledge related to exercise-induced adaptions, including comprehensive changes in the transcriptome, proteome, metabolome, and microbiome, to add new understanding of exercise-induced organ response. Prior studies have typically either focused on specific organ adaptations to exercise or provided systemic observations to shed light on exercise-mimetic effects. For example, a recent study performed proteomic analysis in exercise-training mice to generate an organism-wide and cell-type-specific secreted proteomics map with 10 tissues, which demonstrated that liver-secreted carboxylesterases mediate exercise-like effects.[17] Moreover, extracellular vesicle (EV) studies have shown that the liver plays a central role in exercise responses, as evidenced by EV localization to the liver and cargo transfer to other organs.[18] Another interesting insight from this study is that exercise durations, such as acute *vs.* long-term exercise, induce distinct gene expression profiles and molecular response patterns. As indicated by this study, long-term exercise triggered significant transcriptomics changes in peripheral blood cells and neutrophils with less individual variation compared to acute exercise. This indicates that while short-term or acute exercise tends to induce alterations in proteins and metabolic products, it has a harder time making a "genetic imprint". It remains unclear whether long-term intermittent acute exercise shows similar effects. Together, the recent work by Geng et al.[13] advances our understanding of how exercise-induced organ crosstalk mediates protective effects. Notably, the question of which organ is most critical may not have a simple answer but rather may depend upon contextual physiological conditions.

Nevertheless, some questions remain and should be further explored following the study by Geng et al.[13] Firstly, whether betaine supplementation could exert organ-specific protection against pathological injury independent of aging should be further investigated. Secondly, sex-specific differences between females and males in response to betaine or similar exercise mimetics still require further attention; in particular, researchers should consider increasing the sample size of human subjects. Finally, given the impressive systemic effects of betaine, its role in activating various silent cells with little proliferative potential, such as cardiomyocytes to promote cardiac regeneration, is of great interest. With the development of novel bio-technology and databases,[19] more insightful advances may promote answers to these questions.

In conclusion, by using muti-omics, including single-cell transcriptome, metabolome, proteome, and microbiome,

the study by Geng et al.[13] examines the products from multi-dimensional samples. It identifies the natural, kidney-synthesized compound betaine as an exercise mimetic that exerts cross-organ protection in aged mice, thus providing a promising strategy for promoting healthy aging. Mechanistic investigations also provide insight into the crucial target gene, TBK1, which provides important anti-inflammatory and cellular senescent avenues. Further investigations are needed when betaine is used clinically: (a) to evaluate its clinical safety and potential adverse effects when used as an exercise mimetic; (b) to elucidate the balance between the therapeutic potential of betaine and its potential adverse effects.

Authors' contributions

HW, XY, CJ, TSB, and JX drafted, reviewed, and edited the manuscript. All authors have read and approved the final version of the manuscript, and agree with the order of presentation of the authors.

Declaration of competing interest

The authors declare that they have no competing interests.

Acknowledgments

This work was supported by the National Key Research and Development Project (2022YFA1104500 to JX), the National Natural Science Foundation of China (82020108002 and 82225005 to JX and 82370277 to HW), and the Science and Technology Commission of Shanghai Municipality (23ZR1422900 to HW and 23410750100 to JX). TSB was supported by a Biotechnology and Biological Sciences Research Council (BBSRC) International Partnering Award.

References

1. Burtscher J, Strasser B, D'Antona G, Millet GP, Burtscher M. How much resistance exercise is beneficial for healthy aging and longevity? *J Sport Health Sci* 2023;**12**:284–6.
2. Booth FW, Roberts CK, Laye MJ. Lack of exercise is a major cause of chronic diseases. *Compr Physiol* 2012;**2**:1143–211.
3. Hawley JA, Joyner MJ, Green DJ. Mimicking exercise: What matters most and where to next? *J Physiol* 2021;**599**:791–802.
4. Gao J, Song J, Yan Y, et al. Exercise training-induced microrna alterations with protective effects in cardiovascular diseases. *Rev Cardiovasc Med* 2023;**24**:251. doi:10.31083/j.rcm2409251.
5. Wang L, Wan W, Zhang S, Keswani T, Li G, Xiao J. RNA-mediated epigenetic regulation in exercised heart: Mechanisms and opportunities for intervention. *Mol Aspects Med* 2024;**97**:101274. doi:10.1016/j.mam.2024.101274.
6. Hu J, Miao X, Yu LH. Long non-coding RNAs in diabetic cardiomyopathy: Potential function as biomarkers and therapeutic targets of exercise training. *J Cardiovasc Transl Res* 2025;**18**:1650–66.
7. Wang H, Xie Y, Guan L, Elkin K, Xiao J. Targets identified from exercised heart: Killing multiple birds with one stone. *NPJ Regen Med* 2021;**6**:23. doi:10.1038/s41536-021-00128-0.
8. Bettariga F, Taaffe DR, Galvao DA, et al. Exercise training mode effects on myokine expression in healthy adults: A systematic review with meta-analysis. *J Sport Health Sci* 2024;**13**:764–79.
9. Narkar VA, Downes M, Yu RT, et al. AMPK and PPARdelta agonists are exercise mimetics. *Cell* 2008;**134**:405–15.
10. Richter EA, Kiens B, Wojtaszewski JF. Can exercise mimetics substitute for exercise? *Cell Metab* 2008;**8**:96–8.
11. Goodyear LJ. The exercise pill—Too good to be true? *N Engl J Med* 2008;**359**:1842–4.
12. Fan W, Evans RM. Exercise mimetics: Impact on health and performance. *Cell Metab* 2017;**25**:242–7.
13. Geng L, Ping J, Wu R, et al. Systematic profiling reveals betaine as an exercise mimetic for geroprotection. *Cell* 2025;**188**:5426–8.
14. Mogilnicka I, Kopacz W, Jaworska K, Alramadhan Z, Ufnal M. Urea, TMAO, betaine and other osmolytes as endogenous diuretics in heart failure and hypertension. *Heart Fail Rev* 2025;**30**:1061–74.
15. Luo D, Wang X, Cao S, Ba L, Chen J. Recent advances in betaine: Extraction, identification, and bioactive functions in human health. *Food Sci Nutr* 2025;**13**:e70173. doi:10.1002/fsn3.70173.
16. Cienkowski K, Cienkowska A, Kupczynska K, Bielecka-Dabrowa A. The role of gut microbiota and its metabolites in patients with heart failure. *Biomedicines* 2024;**12**:894. doi:10.3390/biomedicines12040894.
17. Wei W, Riley NM, Lyu X, et al. Organism-wide, cell-type-specific secretome mapping of exercise training in mice. *Cell Metab* 2023;**35**:1261–79.
18. Whitham M, Parker BL, Friedrichsen M, et al. Extracellular vesicles provide a means for tissue crosstalk during exercise. *Cell Metab* 2018;**27**:237–51.
19. Pan L, Ai S, Shi X, et al. ExerGeneDB: A physical exercise-regulated differential gene expression database. *J Sport Health Sci* 2025;**14**:101027. doi:10.1016/j.jshs.2025.101027.