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LETTER TO THE EDITOR

- 30 Fuzhuan brick tea affects obesity process by modulating gut microbiota

Li ZP, Xu DH, He LP, Wang XJ

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Editorial Board Member of *World Journal of Gastrointestinal Pharmacology and Therapeutics*, Chao Sun, MD, PhD, Associate Chief Physician, Associate Professor, Department of Gastroenterology and Hepatology, Tianjin Medical University General Hospital, Tianjin 300052, China. chaosun@tmu.edu.cn

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Fuzhuan brick tea affects obesity process by modulating gut microbiota

Zhi-Peng Li, Dong-Hui Xu, Lian-Ping He, Xin-Juan Wang

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Zhi-Peng Li, Dong-Hui Xu, Lian-Ping He, Xin-Juan Wang, School of Medicine, Taizhou University, Taizhou 318000, Zhejiang Province, China

Corresponding author: Xin-Juan Wang, MD, Senior Researcher, Teacher, School of Medicine, Taizhou University, No. 1139 Shifu Avenue, Taizhou 318000, Zhejiang Province, China.
wxjyxy@tzc.edu.cn

Abstract

The effect of Fuzhuan brick tea (FBT) on metabolism in obese mice is mediated by regulation of N-methyltransferase by aryl hydrocarbon receptor. The expression of the phosphatidylethanolamine N-methyltransferase gene is regulated by many transcription factors, and those specific to this effect need further investigation. Experimental animal studies have been designed to observe the effects of a single drug or the sequential effects of drugs. A washout period should be included if different drugs (*e.g.*, antibiotics and FBT) are given to avoid or reduce additive effects or synergy. Currently, most experimental studies performed in mice used only male animals. However, experience has revealed that the results of using only male mice are very likely to have sex differences.

Key Words: Intestinal flora; Mice; Tea; Sex bias; Fuzhuan brick tea

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Core Tip: Some studies found that Fuzhuan brick tea has an effect on the gut microbiome. Many transcription factors regulate the expression of the phosphatidylethanolamine N-methyltransferase gene. Only selecting aromatic hydrocarbon acceptors for research needs to be given a sufficient basis. In germ-free mice, sex differences in metabolism were reduced, *i.e.*, antibiotics may cause changes in the homogeneity of the mice, and if the mice are of different sexes, the gut microbiota of the mice may be different. Under the influence of antibiotics, sex differences in the microbiota may be reduced or even flattened.

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TO THE EDITOR

We were pleased to read the research article by Liu *et al*[1]. They conducted a study of the effects of Fuzhuan brick tea (FBT) on metabolism in a mouse model of obesity induced with a high-fat diet. They found that FBT had an impact on intestinal microbes. Most importantly, they pointed out that the beneficial effects of FBT on metabolism were strongly correlated with the intestinal flora of the mice. This article provides very detailed research and data analysis, study background, and very clear figures, and the results are reasonable. However, we believe that the study has issues worthy of further discussion.

The authors mentioned that abnormal levels of serum phosphatidylcholines (PCs) and/or a decreased PC to phosphatidylethanolamine (PE) ratio (PC/PE) are risk factors for obesity. Phosphatidylethanolamine N-methyltransferase (PEMT) catalyzes poor synthesis of PC or restricted conversion of PE to PC, which may be one of the factors responsible for abnormal metabolism of PC and PE. Many transcription factors are known to regulate the expression of the *PEMT* gene[2]. What was the basis for choosing only aryl hydrocarbon receptors? We recommend that the authors perform RNA sequencing to analyze the specific transcription factors regulated by PEMT. In addition, we also recommend that the authors provide the corresponding experimental steps so that subsequent works can replicate this experiment. Additionally, both Bernhard[3] and Tseng and Wu[4] reported that the effects of the human gut microbiome on host metabolism and inflammation greatly contribute to an increased risk of obesity. Therefore, high expression of inflammatory factors and abnormal metabolism constitute a high risk of obesity. We suggest that the authors explore the relationship between inflammatory factors and PEMT to strengthen their results and improve the study credibility.

All 35 mice used in the study were male, which ignored the impact of sex differences on the intestinal flora. Although male mice are more widely used in scientific research, this phenomenon generally only appears in the field of brain research. Investigators have increasingly found that the view that women are more "emotional and unstable", introduced in the 19th century, and having a strong influence on research design, falls short. The American neurologists Shansky and Murphy[5] explained that "do not use female animals for the primary reason for the research is that the influence of female hormones complicates many factors, especially when studying the brains of female animals." Problems caused by sex differences in response to drug treatment and difference in the misdiagnosis rate are recognized in fields other than neurology[6,7]. Some drugs are more effective in men than in women, such as the common anti-inflammatory drugs paracetamol and naproxen; others, such as alosetron, which treats acute diarrhea, is not effective for most men. In addition, Weger *et al*[8] described sex-specific differences in gene expression and metabolism that require the presence of microbiota. In germ-free mice, sex differences in metabolism were reduced. Male mice metabolized more like female mice, and female mice metabolized more like males. Antibiotics may cause changes that also introduce homogeneity in mice, and the intestinal flora of mice may be different if the sex of the mouse is different [9]. Under the influence of antibiotics, sex differences in microbiota are likely to be reduced or even flattened. Therefore, we suggest that the authors supplement their results with data obtained from a repeat study including a group of female mice.

In the experimental design, mice treated with antibiotics did not undergo a short washout period of 1-3 d, to eliminate the possible overlapping effects of antibiotics and FBT. Yi *et al*[10] found that polyphenols, the main active ingredient in tea, inhibited or killed intestinal bacteria, especially *Streptococci*. Koo and Cho[11] reported that tea reduced the absorption of cholesterol and lipids from the gastrointestinal tract, which synergistically interacted to improve disease state. Kiss *et al*[12] reported that the ingredients in tea affected the absorption of amoxicillin, thereby reducing its effectiveness. We thus suggest that the authors consider adding a transition period in the experimental design to avoid overlapping or interference between the effects of antibiotics and FBT.

We believe that analysis of the FBT components extracted in only one solvent was not comprehensive enough and may be a limitation, as the composition of FBT is complex, including both fat-soluble and water-soluble components. There may also be some kind of cross-linking between the components. We believe that these factors should all be taken into account.

FOOTNOTES

Author contributions: Li ZP and Xu DH performed the conceptualization, formal analysis, and writing of the original

draft; He LP and Wang XJ contributed to the writing, reviewing, and editing of the manuscript; all authors participated in drafting the manuscript and all have read, contributed to, and approved the final version of the manuscript.

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Country/Territory of origin: China

ORCID number: Zhi-Peng Li 0000-0002-0355-7889; Dong-Hui Xu 0000-0002-4365-9257; Lian-Ping He 0000-0002-9627-5599; Xin-Juan Wang 0000-0002-3888-2016.

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