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**Fu Brick Tea affects obesity process by modulating gut microbiota**

FBT affects obesity process by modulating gut microbiota

Zhipeng Li, Donghui Xu, Lianping He, Xinjuan Wang

## **Abstract**

Effect of Fu Brick Tea (FBT) on metabolism in obese mice was mediated by regulation of N-methyltransferase by aryl hydrocarbon receptor. Phosphatidylethanolamine N-methyltransferase (PEMT) gene has many transcription factors, and those specific to this effect need further investigation. Experimental animal studies are 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. Therefore, the results obtained using only 35 male mice in this study may also be sex-biased.

**Key Words:** Intestinal flora; Mice; Tea; Sex bias

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**Core Tip:** Some study found that FBT has an effect on the gut microbiome. Many transcription factors regulate the expression of the Phosphatidylethanolamine N-methyltransferase gene. Only the selection of aromatic hydrocarbon acceptors 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.

## **TO THE EDITOR**

We were pleased to read the research article by Liu *et al*<sup>[1]</sup>. They conducted a study of the effects of Fuzhuan brick tea (FBT) on metabolism in a mouse model of obesity

induced by 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.<sup>[2]</sup> What was the basis for choosing only aryl hydrocarbon receptor? 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<sup>[3]</sup> and Tseng and Wu<sup>[4]</sup> reported that the effects of the human gut microbiome on host metabolism and inflammation greatly contribute to 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; none were female, which ignores 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 R. M. Shansky<sup>[5]</sup> 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<sup>[6, 7]</sup>. Some drugs are more effective in men than 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*<sup>[8]</sup> 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 in summary, the intestinal flora of mice may be different if the sex of the mouse is different<sup>[9]</sup>. 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 days, to eliminate the possible overlapping effects of antibiotics and FBT. S. Yi *et al*<sup>[10]</sup> found that polyphenols, the main active ingredient in tea, inhibited or kill intestinal bacteria, especially streptococci. Koo and Cho<sup>[11]</sup> reported that tea reduced the absorption of cholesterol and lipids from the gastrointestinal tract, which synergistically interacted to improve disease. Kiss *et al*<sup>[12]</sup> reported that the ingredients in tea affected the absorption of amoxicillin, thereby reducing its effectiveness of the drug. 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.

Antibiotics may cause changes in homogeneity in mice. If the mice are of different sexes, the gut microbiota of mice may be different. Under the influence of antibiotics, the sex differences in the microbiota may be reduced or even flattened.

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