Synbiotics inhibits gut microbiome perturbation-caused prolongation of migraine-like pain by restoring short-chain fatty acid signaling

背景介绍

Migraine is the most common disabling primary headache disorder with a high incidence of pain hypersensitivity. However, its exact pathogenesis remains unclear. The gut-brain axis mediates the communication between gastrointestinal (GI) tract and brain through neural, endocrine, metabolic, and immune pathways. Accumulating evidence has suggested that gut microbiome plays an important role in the pathogenesis of migraine. However, how gut microbiome is involved in migraine remains to be investigated. Synbiotics facilitate the production of gut metabolites including SCFAs that regulate the interactions of central nervous system, peripheral nervous system and enteric nervous system, and SCFAs receptors are expressed broadly in these nervous systems. However, which SCFA receptor mediates such effect is still unknown. In the present study, we investigated the effect of synbiotics supplementation on the gut microbiome perturbation-caused prolongation of migraine-like pain and examined whether SCFA signaling contributes to the underlying mechanism.

作者简介

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研究方法

1. Animals: C57BL/6 wild-type mice and Ffar2 knockout mice were used.
2. Nitroglycerin-induced migraine mouse model
3. Antibiotics treatment and synbiotics supplementation
4. Facial mechanical hypersensitivity test
5. 16S rRNA sequencing
6. Fecal SCFA measurement
7. SCFA treatment
8. Histomorphological evaluation
9. Western blotting
10. Immunohistochemistry
11. mRNA sequencing experiment
12. Metabolite extraction and UPLC-MS/MS analysis

研究结果

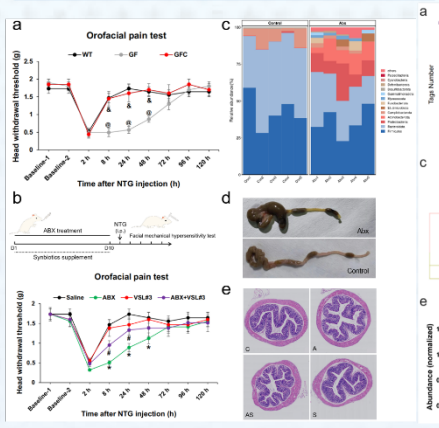

Fig 1. Supplementation with synbiotics inhibits gut microbiome perturbation-prolonged migraine-like pain

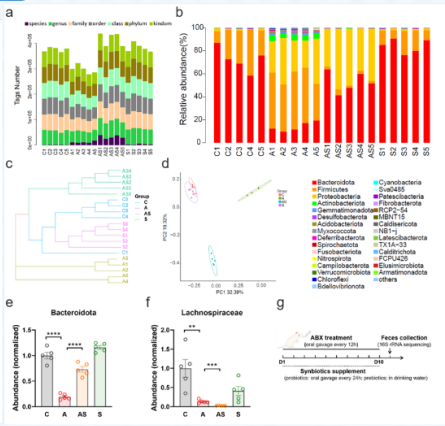

Fig 2. Supplementation with synbiotics reverses ABX-produced gut microbiome perturbation

研究结果

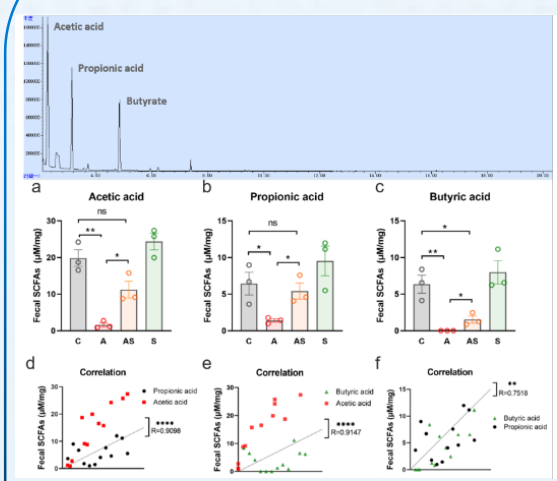

Fig 3. Supplementation with synbiotics diminishes ABX-produced reduction of SCFAs in the gut

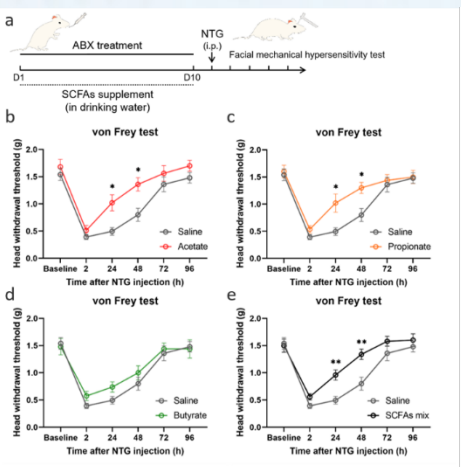

Fig 4. Effects of different SCFAs on gut microbiome perturbation-prolonged migraine-like pain

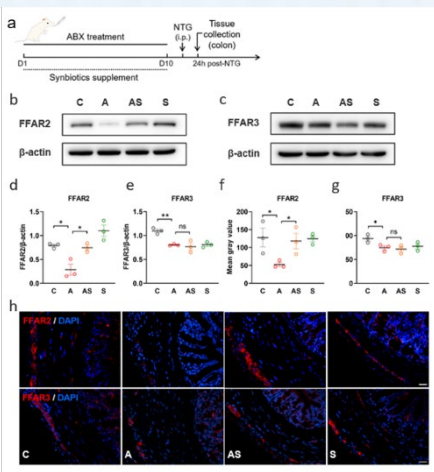

Fig 5. Supplementation with synbiotics restores ABX-decreased expression of SCFA receptor FFAR2, but not FFAR3, in the gut

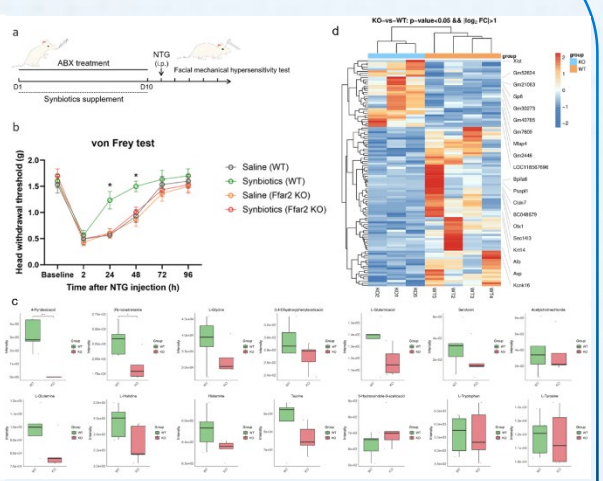

Fig 6. Supplementation with synbiotics inhibits gut microbiome perturbation-prolonged migraine-like pain through FFAR2-mediated SCFA signaling

结 论

In conclusion, our results demonstrate that gut SCFAs, especially acetic acid and propionic acid, as well as SCFAs-FFAR2 signaling are critical for migraine pain chronification, and that the supplementation of synbiotics or relevant SCFAs can be developed into an alternative therapy for chronic migraine pain. Future studies could focus on FFAR2 downstream pathways to identify more specific molecular targets for this pain condition.

致 谢

This work was supported by the National Natural Scientific Foundation of China (82201357) , the Key Science and Technology Program of Henan Province (212102310651), and the Doctoral Scientific Research Foundation of Xinxiang Medical University (YBSKYZZ202004).

代表作

1. Yuanyuan Tang, Juan Du, Hongfeng Wu, et al. Potential Therapeutic Effects of Short-chain Fatty Acids on Chronic Pain. Curr Neuropharmacol. 2024;22(2):191. (2区, IF:5.3)
2. Yuanyuan Tang, Sufang Liu, Hui Shu, et al. Gut Microbiota Dysbiosis Enhances Migraine-Like Pain Via TNFα Upregulation. Mol Neurobiol. 2020,57(1):461. (2区, IF:5.59)
3. Yuanyuan Tang, Sufang Liu, Hui Shu, et al. AMPA receptor GluA1 Ser831 phosphorylation is critical for nitroglycerin-induced migraine-like pain. Neuropharmacology. 2018,133:462. (2区, IF:4.249)