Editorial: involvement of neuro-immune mechanism and brain–gut axis in pathophysi...

Health & Medicine

The Editorial on the Research Topic

Involvement of Neuro-Immune Mechanism and Brain–Gut Axis in Pathophysiology of Mood Disorders

Mood disorders are common and generally recurrent episodic or chronic disorders that present with only depressive symptoms in the case of major depressive disorder (MDD), whereas both depressive and manic symptoms are found in bipolar disorders (BD). Mood disorders cause substantial individual, societal, and economic burden (1), and are the most common diagnosis associated with suicide. The diagnosis of mood disorders depends currently on clinical symptoms. There are no known biological markers to aid the diagnosis of mood disorders. There has been a surge of interest in the inter-relationship between neuro-immunology and gut microbiota in mood disorders. This journal issue examines the potential role of these two domains and their possible interaction in the pathogenesis of mood disorders. Pro-inflammatory cytokine elevation has been reported in mood disorders (2), and they can cross the blood–brain barrier and affect microglial activation (3). On the other hand, gut microbiota has also been associated with mood disorders (4) and can affect the brain by producing neurotransmitters and bacterial metabolites and by promoting the release of pro-inflammatory cytokines (5). Alternations of gut microbiota characteristics, especially an increase in pro-inflammatory genera, are reported in mood disorders (6). The research topic of this current journal issue provides a forum focusing on a set of investigations of the neuro-immune and brain–gut axis mechanisms in mood disorders. It includes

several studies investigating potential biological markers for diagnostic and prognostic prediction in mood disorders.

Liu et al. explored the role of the kynurenine pathway in MDD. Kynurenic acid in a receiver operating characteristic (ROC) curve predicts MDD (82. 5%), and area under the ROC curve remains comparable (83. 6%) for an MDD diagnosis when combining kynurenic acid and quinolinic acid levels. More work is needed to determine the exact role of the kynurenine pathway in the pathogenesis of MDD, and its relevance as a potential treatment target.

A randomized controlled trial by Yang et al. assesses whether endoplasmic reticulum stress (ERS) can mediate an antidepressant effect and serve as a treatment target for depression. The chronic unpredictable mild stress (CUMS)-induced depression rat model displays depressive-like behaviors and an increase in hippocampal cell apoptosis and ERS markers glucose-regulated protein 78 and C/EBP-homologous protein. Antidepressant medications reduced the depressive-like behaviors and ERS marker levels. Therefore, ERS may be a therapeutic target for MDD. Microglia area type of macrophage in central nervous system (CNS) is involved in neuroinflammation (7).

Activated microglia increase pro-inflammatory cytokines in CNS, which in turn could decrease serotonin neurotransmission through kynurenine pathway, and affect cell apoptosis, excitotoxicity, neurogenesis, and neurotrophin production (8). The Tan et al. study employed a CUMS-induced gestating mouse model and microglia-specific autophagy-deficient

mice. Compared to normal mice, the microglia-specific autophagy-deficient mice showed higher inflammatory factors and lower brain-derived neurotrophic factor (BDNF) expression levels and autophagy-associated proteins. Following 3 weeks of fluoxetine administration, depressive behavior was reversed, BDNF levels and autophagy-associated proteins increased, while inflammatory factors decreased.

Previous studies reported that gut microbiota affect microglial maturation and activation, as part of the brain–gut axis (9 , 10). Liu et al. describe the neuro-endocrine-immune mechanisms of the brain–gut axis and summarize findings from animal and human studies that demonstrate their relationship to mood disorders. Alterations of gut microbiota characteristics are found in mood disorders, and administering prebiotics, probiotics, and suitable antibiotics could potentially reverse depressive symptoms. They conclude that although more research is needed, it may be possible to treat mood disorders by selective targeting of gut microbiota in the future.

Cheung et al. further reviewed the relationship between gut microbiota and MDD. Although statistically there were no consistent findings of gut microbiota changes in MDD in human studies, we need to refine our methodologies further to better understand how gut microbiota contribute to the pathogenesis of MDD.

Aizawa et al. focused on Bifidobacterium and Lactobacillus counts in patients with bipolar disorder (BD). Compared to healthy controls, no difference was found in BD regarding Bifidobacterium or Lactobacillus. However, negative correlations were observed between Lactobacillus counts and sleep and

between Bifidobacterium counts and cortisol levels. These microbial taxa may not be associated with emotional symptoms, but with other disease characteristics, such as sleep and stress response. Li et al. investigated the relationship of the gut microbiota to insomnia, circadian disturbance, and depression. The authors offered a hypothesis that low-level chronic inflammation may be linked to sleep loss, circadian misalignment, mood disorders, and metabolic disease.

These studies provide preliminary evidence regarding the potential of biological markers of neuro-immunology and microbial markers to distinguish patients with mood disorders from healthy controls, as well as their potential as therapeutic targets. Longitudinal studies of such potential biological markers in patients will further our understanding of the cause–effect relationship between mood disorders, the gut microbiota, and neuro-immunology and their role in mediating treatment response.

Author Contributions

SH wrote the manuscript. YF, CN, and JM edited the editorial.

Funding

This study was funded in part by grants from the National Key Research and Development Program of China (No. 2016YFC1307104 to S. H. H.) and the Key Research Project of Zhejiang Province (No. 2015C03040 to Y. X.).

Conflict of Interest Statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgments

We thank all authors who contributed to the Research Topic.

References

1. Wittchen HU. The burden of mood disorders. *Science* (New York, NY) (2012) 338(6103): 15. doi: 10. 1126/science. 1230817

PubMed Abstract | CrossRef Full Text | Google Scholar

2. Culmsee C, Michels S, Scheu S, Arolt V, Dannlowski U, Mitochondria AJ, Microglia and immune system—how are they linked in affective disorder? *Front Psychiatry* (2019) 9: 739. doi: 10. 3389/fpsyt. 2018. 00739

PubMed Abstract | CrossRef Full Text | Google Scholar

3. Bhattacharya A, Derecki NC, Lovenberg TW, Drevets WC. Role of neuro-immunological factors in the pathophysiology of mood disorders. *Psychopharmacology (Berl.)* (2016) 233(9): 1623–36. doi: 10. 1007/s00213-016-4214-0

PubMed Abstract | CrossRef Full Text | Google Scholar

4. Dinan TG, Gryan JF. Gut-brain axis in 2016: brain-gut-microbiota axis-mood, metabolism and behavior. *Nat Rev Gastroenterol Hepatol* (2017) 14(2): 69–70. doi: 10. 1038/nrgastro. 2016. 200

PubMed Abstract | CrossRef Full Text | Google Scholar

5. Powell N, Walker MM, Talley NJ. The mucosal immune system: master regulator of bidirectional gut-brain communications. *Nat Rev Gastroenterol Hepatol* (2017) 14(3): 143–59. doi: 10. 1038/nrgastro. 2016. 191

PubMed Abstract | CrossRef Full Text | Google Scholar

6. Huang T-T, Lai J-B, Du Y-L, Xu Y, Ruan L-M, Hu S-H. Current understanding of gut microbiota in mood disorders: an update of human studies. *Front Genet* (2019) 10: 98. doi: 10. 3389/fgene. 2019. 00098

PubMed Abstract | CrossRef Full Text | Google Scholar

7. Boche D, Perry VH, Nicoll JA. Review: activation patterns of microglia and their identification in the human brain. *Neuropathol Appl Neurobiol* (2013) 39(1): 3–18. doi: 10. 1111/nan. 12011

PubMed Abstract | CrossRef Full Text | Google Scholar

8. Watkins CC, Sawa A, Pomper MG. Glia and immune cell signaling in bipolar disorder: insights from neuropharmacology and molecular imaging to clinical application. *Transl Psychiatry* (2014) 4: e350. doi: 10. 1038/tp. 2013. 119

PubMed Abstract | CrossRef Full Text | Google Scholar

9. Mosher KI, Wyss-Coray T. Go with your gut: microbiota meet microglia. *Nat Neurosci* (2015) 18(7): 930–1. doi: 10. 1038/nn. 4051

PubMed Abstract | CrossRef Full Text | Google Scholar

10. Abdel-Haq R, Schlachetzki JCM, Glass CK, Mazmanian SK. Microbiome-microglia connections via the gut-brain axis. *J Exp Med* (2019) 216(1): 41–59. doi: 10. 1084/jem. 20180794

PubMed Abstract | CrossRef Full Text | Google Scholar