Clock-controlled chemokine contributes to neuroinflammation-induced depression

June 8 2020, by Zhang Nannan

Credit: CC0 Public Domain

Depression is a mental disorder with complex gene-environment

interactions. Previous studies have suggested circadian factors play a crucial role in the etiology of depression. Moreover, there is a growing body of evidence supporting neuroinflammation is an important factor involving the pathology of depression.

More interestingly, microglia as the main executor of immune function in the central nervous system rhythmically express inflammatory factors and circadian clock genes. However, the effects of potential interactions between rhythmicity and neuroinflammation on depression remain unknown.

To address this issue, a research team led by Prof. Lin Wenjuan from Center for Key Laboratory of Mental Health at the Institute of Psychology of the Chinese Academy of Sciences has conducted a study to explore whether Per2, a central clock component of circadian output, plays a role in depression by regulating central immune function using a mouse model of depression induced by neuroinflammation.

Ten- to 12-week-old Per2 homozygous mutant ($Per2^{Brdm1}$) male mice and age-matched congenic strains of wild type (WT) C57BL/6J control male mice were used to inject lipopolysaccharide (LPS) intracerebroventricularly in a stereotaxic apparatus with a microsyringe attached to a micro infusion pump, and sterile saline treatments as control group.

The results reveal $Per2^{Brdm1}$ mice were resilient to neuroinflammation-induced depressive behavior. After repeated central LPS injections, chemokines like MCP-1, MIP-1β, and RANTES increased in WT mice but not in $Per2^{Brdm1}$ mice in the hippocampus and media PFC.

In addition, intracerebroventricular injection of RANTES resulted in depression-like behavior, and Met-RANTES, a RANTES antagonist, could reverse this behavior induced by LPS treatments.

There is no change of Per2 expression in both WT and $Per2^{Brdm1}$ mice, while BMAL1 expression decreased only in LPS-treated $Per2^{Brdm1}$ mice after repeated central LPS treatments, suggesting that BMAL1 may mediate the effects of Per2 on depressive behaviors induced by neuroinflammation.

Circadian transcription factor BMAL1 could bind to the promoter of Rantes, which may be a potential mechanism underlying the resilience of $Per2^{Brdm1}$ mice to neuroinflammation-induced depression-like behaviors.

"These results uncover a novel clock-immunological mechanism of neuroinflammation-induced depression and promote our understanding of depression, which may facilitate the development of new therapeutic strategy for inflammation-linked depressive disorders," said Prof. Liu.

This research is now published in The FASEB Journal entitled "The clock-controlled chemokine contributes to neuroinflammation-induced depression."

More information: Xiaojuan Chen et al. The clock-controlled chemokine contributes to neuroinflammation-induced depression, *The FASEB Journal* (2020). DOI: 10.1096/fj.201900581RRR

Provided by Chinese Academy of Sciences