Aggressive or friendly? The inflammatory protein interleukin 1β may decide

May 18 2021

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Aggression is common in many neuropsychiatric diseases, such as dementia, autism spectrum disorder, and schizophrenia. It causes many problems for patients and their families, but can be difficult to treat because little is known about what causes it. In a study published last

month in *Molecular Psychiatry*, researchers from the University of Tsukuba revealed that variation in levels of interleukin 1β (IL-1β), a protein that mediates the inflammatory response, is associated with individual differences in aggressive behaviors in male mice.

In humans, levels of inflammatory proteins such as IL-1β in the blood correlate with aggressive traits. To better understand these findings, researchers at the University of Tsukuba decided to investigate IL-1β levels in the blood of male mice, which they classified as aggressive or non-aggressive based on their behaviors toward other male mice. Unexpectedly, there were no differences in blood IL-1β levels between the aggressive and non-aggressive mice, in contrast to what had been reported in humans. This finding intrigued the researchers, and they wanted to know more.

"The dorsal raphe nucleus is a region of the brain that is important in aggressive behaviors," says lead author of the study Professor Aki Takahashi. "We decided to investigate IL-1β levels in this brain region in mice, and to experiment using drugs and genetic methods to reduce the effects of IL-1β on its receptors, to see if there were any related changes in aggressive behaviors."

The results were surprising: IL-1β was actually lower in the dorsal raphe nucleus of aggressive mice than in non-aggressive mice. In addition, in the experiments where IL-1β was less able to act on its receptors in this brain region, the mice were more aggressive.

The researchers then decided to look at the relationship between IL-1β and serotonin, a key neurotransmitter in the control of aggression. They found that, during aggressive encounters, serotonin neurons in the dorsal raphe nucleus were more active in aggressive mice than in non-aggressive mice. Moreover, when they experimentally lowered the expression of IL-1 receptors, serotonin neurons were also more active in

this brain region.

"Our findings suggest that IL-1β in the dorsal raphe nucleus suppresses aggressive behavior, possibly by acting on the serotonin system," says Takahashi.

The findings suggest that IL-1β and serotonin neurons might be potential drug targets for reducing aggression, which currently has few effective treatments. The results of this study could therefore lay the foundations for research into treatment approaches for aggression in patients with neuropsychiatric diseases.

More information: Aki Takahashi et al. Neuromodulatory effect of interleukin 1β in the dorsal raphe nucleus on individual differences in aggression, *Molecular Psychiatry* (2021). DOI: 10.1038/s41380-021-01110-4

Provided by University of Tsukuba