Two competing proteins affect the chronic inflammation of the nervous system following viral infection

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Figure 1: Inflammation of the central nervous system following a viral infection can lead to fatigue and depression depending on the competing activity of two cytokine proteins. Credit: imtmphoto/iStock/Thinkstock

Fatigue and depression are common during and after viral infection, and in some cases can become chronic long-term ailments. Fever and inflammation associated with viral infections are triggered by the release of proinflammatory proteins called cytokines. These proteins can also trigger persistent inflammation of the central nervous system, or neuroinflammation, which is thought to be a key factor in the onset of viral-related depression and fatigue. The exact molecular mechanisms involved, however, are not fully understood.

Yosky Kataoka, Masanori Yamato and colleagues from the RIKEN Center for Life Science Technologies have now uncovered the roles of two cytokines, interleukin 1 beta (IL-1?) and its receptor antagonist IL-1ra, in triggering and controlling neuroinflammation in rats.

When faced with viral infection, the body's immune system responds by releasing cytokines. Overexpression of specific cytokines known as interferon alpha (IFN-?) in the brain can trigger long-term neuroinflammation. Previous research has shown that injecting animals with a synthetic double-stranded RNA called poly I:C, which mimics the activity of a virus in the body, induces a decrease in behavioral activity caused by IFN-? overexpression in the brain. Kataoka's team conducted a series of experiments involving poly I:C injection in rats, and found that levels of spontaneous behavior in the rats fell significantly after injection, yet showed signs of recovery after a week.

"We wanted to expand on previous studies and work out which mechanisms tip the balance towards more chronic problems," says Kataoka. "We focused on two main cytokines, IL-1?, and its competing molecule IL-1ra."

By injecting IL-1? into the rat brain, the team generated the same dip in spontaneous activity as observed following poly I:C injection, showing that IL-1? was responsible for inducing the production of IFN-? and therefore influencing levels of neuroinflammation. "We also noted that IL-1ra is a functional regulator of IL-1?," mentions Kataoka.

The researchers demonstrated that blocking the efficacy of IL-1ra in the brain delayed the rats' recovery still further. Infusion of IL-1ra into the brains of rats injected with poly I:C, on the other hand, arrested the depressive behavior.

"These results indicate that IL-1ra has an important role in preventing neuroinflammation entering a chronic state," explains Kataoka. "Maintaining a careful balance in the production of IL-1? and IL-1ra

is therefore crucial for healthy brain function."

More information: Yamato, M., Tamura, Y., Eguchi, A., Kume, S., Miyashige, Y., Nakano, M., Watanabe, Y. & Kataoka, Y. "Brain interleukin-1? and the intrinsic receptor antagonist control peripheral Toll-like receptor 3-mediated suppression of spontaneous activity in rats." *PLoS ONE* 9, e90950 (2014).
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