PERSPECTIVE

Fatigue sensation following peripheral viral infection is triggered by neuroinflammation: who will answer these questions?

Fatigue is best defined as difficulty in initiating or sustaining voluntary activities, and is thought to be accompanied by deterioration of performance. Fatigue can be caused by many factors such as physical and mental stress, disturbance in the circadian rhythm, and various diseases. For example, following the flu or other types of infections, everyone has experienced a sense of fatigue that can last for days or weeks. The fatigue sensation is thought to be one of the signals for the body to suppress physical activity in order to regain health. The mechanism of induction of the fatigue sensation following viral infection has not been well understood. Although fatigue was once thought to be caused by fever, our recent study with an animal model of viral infection demonstrated that the fatigue sensation is caused not by fever, but rather, by neuroinflammation of brain tissue (Yamato et al., 2014). A positron emission tomography (PET) study in patients with chronic fatigue syndrome/myalgic encephalomyelitis revealed that activation of microglia is involved in neuroinflammation in the brain, and indicated that the intensity of the PET signals evaluating the presence of neuroinflammation was associated with the severity of neuropsychological symptoms (Nakatomi et al., 2014). Other studies have indicated that neuroinflammation is an important precipitating event in chronic neurological disorders including Alzheimer's disease, Parkinson's disease, and depression (Song and Wang, 2011; Fan et al., 2014). Therefore, an understanding of the regulatory mechanisms of neuroinflammation and the prevention of entering the chronic state is important.

Peripheral viral infection affects the central nervous system: Viral infections such as influenza cause the occurrence of acute inflammation, and pro-inflammatory cytokines including interleukin (IL)-1β and/or antiviral cytokines including interferons (IFNs) are produced by activation of Toll-like receptors (TLRs) in the periphery. Even during a peripheral infection, not only fever is experienced, but also abnormal psychological and somatic feelings, including fatigue sensations, depressive feeling, and cognitive impairment, as well as anorexia and muscle and/or joint pain. Peripherally-produced cytokines have been thought to act on the central nervous system through multiple routes as follows: (i) meningeal macrophages, cerebral endothelial cells, and perivascular microglial cells; (ii) cells in circumventricular organs such as the organum vasculosum of the lamina terminalis and the area postrema, which lack a functional blood-brain barrier; and (iii) vagal afferent nerves that innervate the nucleus of the solitary tract in the brain stem, projecting catecholaminergic fibers to the hypothalamus. Such afferent transductions of inflammatory signals are thought to induce activation of immunologically responsive cells such as microglia and cytokine expression in the brain (**Figure 1**).

Cytokines in the brain suppress spontaneous activity in animals: Intraperitoneal (i.p.) injection of polyriboinosinic: polyribocytidylic acid (poly I:C), a synthetic double-stranded RNA, is known to mimic viral infection in experimental animals. Injected poly I:C is recognized by Toll-like receptor 3 (TLR3), which is expressed in macrophages, dendritic cells, and intestinal epithelial cells in the periphery (**Figure 1**). TLR3 uses the Toll-like receptor adaptor molecule 1 (TICAM-1), an adaptor molecule, to activate interferon regulatory factor 3 (IRF3) and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), the downstream molecules, and induces production of anti-viral type I IFNs and inflammatory cytokines such as IL-1β, IL-6, and tumor necrosis factor alpha (TNF-α). Katafuchi et al. reported that peripheral injection of poly I:C suppressed voluntary running wheel activity for more than a week following transient fever in rats. Poly I:C injection induced prolonged upregulation of IFN-α mRNA in the cerebral cortex, hippocampus, and hypothalamic regions continuing for more than a week. Katafuchi et al. also showed that IFN-α in the brain modulates the serotonergic system by increasing serotonin (5-HT) transporters, and that 5-HT_{1A} receptor agonist administration attenuated the poly I:C-induced decrease in running wheel activity (Katafuchi et al., 2005). These observations suggest that the production of IFN-α induces fatigue-like behavior by suppression of the serotonergic system. We also induced neuroinflammation by intraperitoneal injection of poly I:C in rats, and then investigated how the neuroinflammation was caused and regulated. The rats showed transient fever and prolonged suppression of spontaneous activity for several days following poly I:C injection. NS-398, a cyclooxygenase-2 (COX-2) inhibitor, completely prevented fever, but did not improve spontaneous activity, indicating that suppression of spontaneous activity was not induced by the arachidonate cascade that generated the fever. The animals overexpressed IL-1β and IL-1 receptor antagonist (IL-1ra) in the brain including

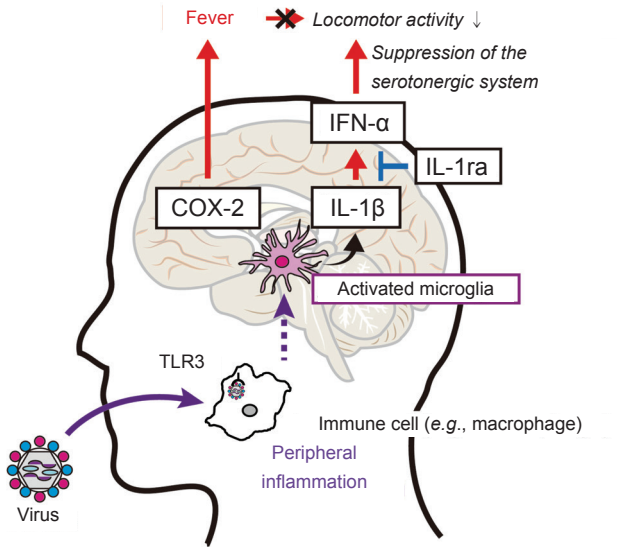

Figure 1 Molecular mechanism of transient fever and suppression of locomotor activity following viral infection.
Suppression of locomotor activity is caused not by cyclooxygenase-2 (COX-2) production involved in fever, but by neuroinflammation including production of interleukin (IL)-1β by activated microglia. The balance of IL-1β and IL-1ra production regulates the extent and duration of neuroinflammation. IFN-α: Interferon-α; TLR3: toll-like receptor 3.

the cerebral cortex. Blocking the IL-1 receptor in the brain by intracerebroventricular (i.c.v.) infusion of recombinant IL-1ra completely blocked the poly I:C-induced suppression of spontaneous activity and attenuated amplification of brain IFN-α expression (**Figure 1**).

Balance of IL-1β and IL-1 receptor antagonist controls behavior following viral infection: The IL-1ra is a member of the IL-1 family that binds to IL-1 receptors, but does not induce an intracellular response. Loddick et al. (1997) demonstrated that i.c.v. injection of anti-IL-1ra antiserum aggravates brain lesions induced by middle cerebral artery occlusion (MCAO) in rats, indicating that endogenous IL-1ra shows a neuroprotective effect in the brain. In our study, IL-1ra mRNA was overexpressed in the brain following poly I:C injection, and the expression pattern against time was similar to that of IL-1β, especially in the cerebral cortex in rats. We also demonstrated that i.c.v. infusion of neutralizing antibody against IL-1ra significantly delayed recovery from decreased spontaneous activity induced by poly I:C injection. These results suggest that endogenous IL-1ra in our brain prevents the shift from acute inflammation to the chronic state following transient virus infection. Therefore, the impairment of IL-1ra production in the brain could induce chronic neuroinflammation, and the balance of IL-1β and IL-1ra production in the brain is possibly involved in the pathogenesis of neurological disorders. We hypothesize that the localized pattern and different processes of neuroinflammation in the central nervous system make variations of neurological disorders.

Possibility of minocycline to improve fatigue sensation induced by neuroinflammation: Minocycline is a semi-synthetic second generation derivative of tetracycline. Minocycline can be absorbed rapidly and can penetrate the blood-brain barrier. In the past decade, minocycline has been shown to exert biological effects other than its antimicrobial action in experiments with cells or animals: suppression of the blood-brain barrier breakdown *via* suppression of matrix metalloproteinase (MMP)-9 production, alleviation of white matter injury in the neonatal rat brain *via* inhibition of IL-1β and TNF-α expression, neuroprotection from ischemic injury or contusion injury, attenuation of microglial activation, suppression of NOx production in cultured microglia under hypoxia, and alleviation of lipopolysaccharide-induced depressive-like behavior (Garrido-Mesa et al., 2013). In our study, we demonstrated that pretreatment with minocycline (20 mg/kg) attenuated poly I:C-induced IL-1β expression in the brain, transient fever, and decrease in locomotor activity in rats (Kataoka et al., 2013). Further, Yasui et al. (2014) recently reported that intratrathecal administration of minocycline alleviated muscular hyperalgesia and mechanical allodynia by suppression of microglia activation in the spinal cord of a rat model for chronic fatigue syndrome. These observations suggest that neuroinflammation is involved in symptoms of viral infection and/or chronic fatigue syndrome.

Although the mechanisms of the suppressive effect on neuroinflammation by minocycline are not fully understood, several clinical trials of minocycline for use in neurological disorders including acute stroke (Kohler et al., 2013) have been conducted. However, reports from some of these clinical trials have not yet shown any positive effects. Once severe neuroinflammation occurs, it might be difficult to suppress it easily. Indeed we could not demonstrate the suppressive effect on neuroinflammation by minocycline after injection of poly I:C to rats. Further understanding of the molecular mechanisms involved in the action of minocycline on neuroinflammation is required for utilizing its full therapeutic potential. Controlling neuroinflammation will bring about alleviation of the fatigue sensation and sluggishness, and prevention of the progression of neurological disorders.

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