

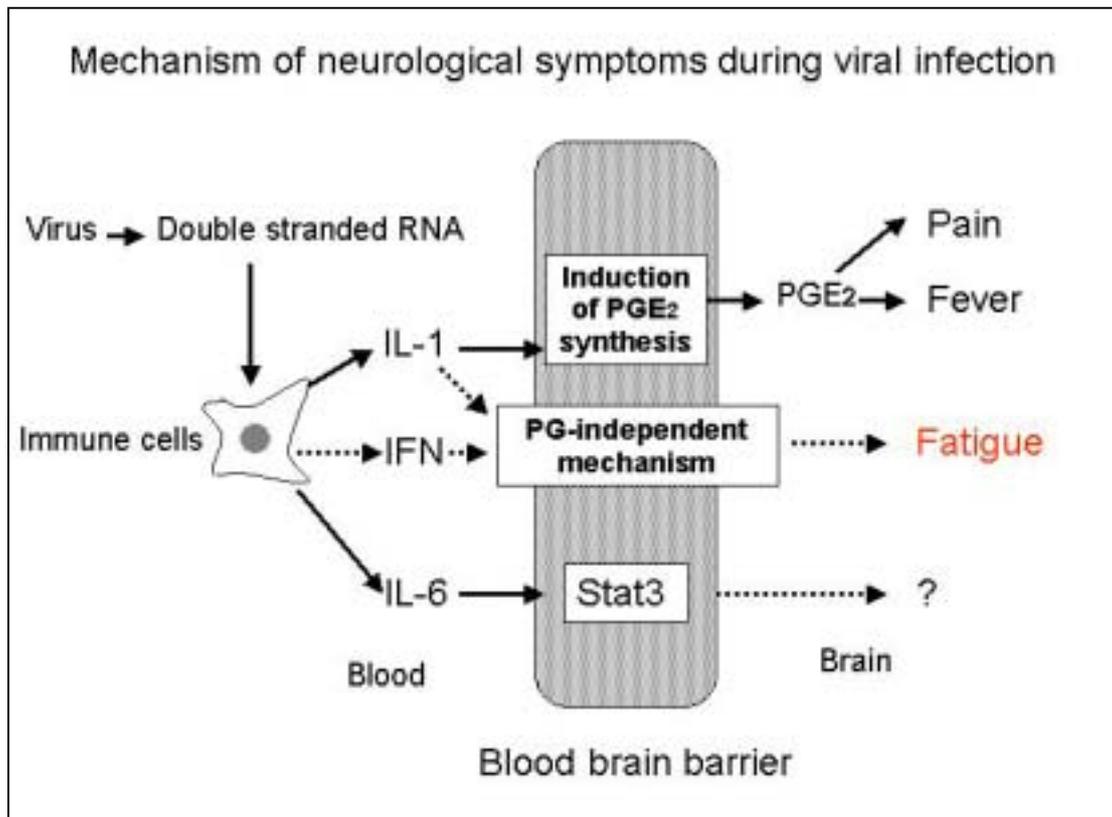
Neuro-immune mechanisms of fatigue during viral infection

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Viral infection is accompanied by a set of neurological symptoms including fever, fatigue, pain, loss of appetite, and sleepiness. These symptoms are brought about by the immune-brain signaling, in which multiple cytokines are thought to play the mediator role. However, it is not clarified yet how each cytokine acts on the brain, and how particular neuronal sets are activated or inhibited by the cytokines to evoke the neurological symptoms. To answer these questions, we employed rodent models of viral infection, in which poly IC (synthetic double-stranded RNA) was injected intraperitoneally in rats or mice. In these models, we have been studying mechanisms of fatigue and fever from various aspects of neuro-immune response, including (i) behavioral and neuronal responses, (ii) prostaglandin production in the brain, and (iii) cytokine production and their action on the brain. Results we have obtained are summarized as follows.

- Poly IC evoked fever and behavioral suppression (fatigue) in rats.
- Poly IC-induced fever was prostaglandin-dependent because a cyclooxygenase-2 (COX-2) inhibitor blocked the fever. Poly IC induced expressions of COX-2 and its downstream enzyme, *i.e.*, prostaglandin E synthase (PGES) in brain endothelial cells. Thus, brain endothelial cells are the sites of PGE₂ biosynthesis.
- On the other hand, behavioral suppression was not inhibited by a COX inhibitor indicating that behavioral suppression is mediated through a PG-independent mechanism. In line with this observation, there were two groups of neurons in the brain, one expressing cFOS in PG-dependent manner and the other expressing cFOS in PG-independent manner.
- Poly IC elevated plasma levels of IL-1beta and IL-6.
- IL-6 acted on brain endothelial cells and translocated STAT3 to the nucleus. However, IL-6 unlikely played an essential role in the behavioral suppression because IL-6-deficient mice normally responded to poly IC with behavioral suppression.
- We are currently working on a hypothesis that IL-1beta and interferons (IFNs) are essential to poly-IC-induced fatigue.



Publications

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