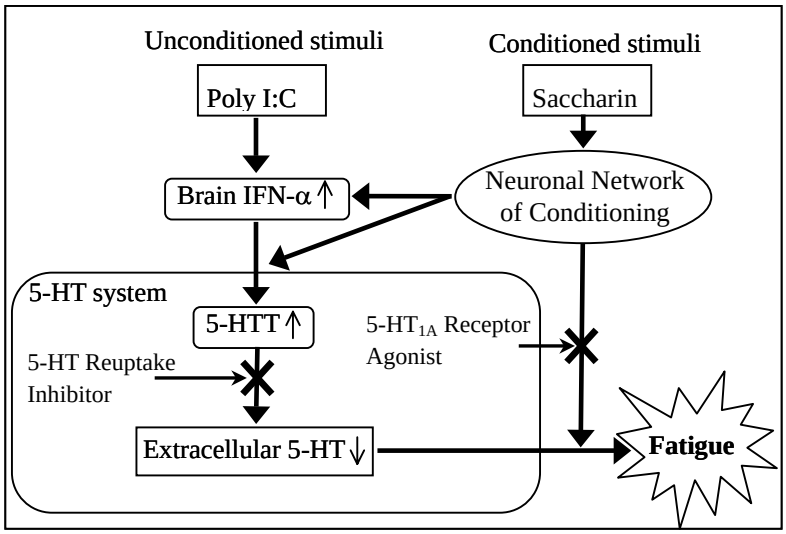
Brain IFN-α and serotonin system in immunologically induced fatigue

Toshihiko Katafuchi

Department of Integrative Physiology, Graduate School of Medical Sciences,

Kyushu University, Fukuoka, 812-8582, Japan

The immunologically induced fatigue was conducted in rats by intraperitoneal (IP) injection of a synthetic double-stranded RNAs, poly I:C. An IP injection of poly I:C (3 mg/kg) decreased the daily amounts of spontaneous running wheel activity to about 40-60% of the preinjection level until day 9, then gradually returned to the baseline level by day 14. In the open field test, the locomotor activity of the poly I:C-injected rats decreased on day 1, but it was not different from the saline-injected group on day 7, suggesting that the poly I:C-induced fatigue on day 7 was not due to the peripheral problems such as muscle/joint pain, but involved the central nervous system. Quantitative analysis of mRNA levels using a real-time capillary reverse transcriptase (RT)-PCR method revealed that the amount of mRNA for interferon-α (IFN-α) increased in the medial preoptic, paraventricular, ventromedial hypothalamic nuclei, and cortex on day 1 and even day 7. Serotonin transporter (5-HTT) mRNA, which is known to be induced by IFN-α in astrocytes, also increased in the same brain regions on day 7. Interleukin-1β (IL-1β) and inhibitor of nuclear factor κB (I-κB) mRNAs increased on day 1, but recovered within a week. In vivo brain microdialysis revealed that the extracellular concentration of 5-HT in the prefrontal cortex decreased after poly I:C injection. Since this decrease in 5-HT was blocked by selective 5-HT reuptake inhibitor, fluoxetine, it was thought to be due to an enhanced expression of 5-HTT. Furthermore, the poly I:C-induced suppression of the running wheel activity was attenuated by 5-HT1A receptor agonist, 8-hydroxy-2-(di-n-propylamino) tetraline (8-OH-DPAT). Finally, the poly I:C-induced decrease in activity was conditioned using poly I:C (ip) as an unconditioned stimulus and saccharin drinking as a conditioned stimulus, and this conditioned response was completely blocked by 8-OH-DPAT, indicating the presence of neuronal circuit for the central fatigue. These findings, take together, suggest that brain IFN-α and 5-HT system play an important role in the neuronal mechanisms of the immunologically induced fatigue by poly I:C.


Unconditioned stimuli
Conditioned stimuli
Poly I:C
Saccharin
Brain IFN-α ↑
Neuronal Network of Conditioning
5-HT system
5-HTT ↑
5-HT1A Receptor Agonist
5-HT Reuptake Inhibitor
Extracellular 5-HT ↓
Fatigue