The Study for the pathophysiology of Chronic Fatigue Syndrome

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Chronic fatigue syndrome (CFS) is an operational concept to clarify the unknown etiology of the syndrome characterized by the abnormally prolonged fatigue. Recently, we found that most CFS patients showed low levels of serum acetylcarnitine, which correlates closely with the fatigue rating score, and that a significant quantity of acetyl moiety of serum acetylcarnitine is taken up into the brain. Metabolite analysis of the mouse brain revealed that an acetylcarnitine taken up into the brain is mainly utilized for the biosynthesis of glutamate. When we studied the cerebral uptake of acetylcarnitine by using [2-^{11}C]acetyl-L-carnitine, a significant decrease was detected in several regions in CFS group, namely in the prefrontal and temporal cortices, anterior cingulate and cerebellum (Fig. 1). These findings suggest that the levels of biosynthesis of neurotransmitters through acetylcarnitine might be reduced in some regions of the brain of CFS patients and that this abnormality might be one of the key elements to unveiling the mechanisms of the chronic fatigue sensation. Furthermore, when we examined a serotonin transporter (5-HTT) gene promoter polymorphism, which affects the transcriptional efficiency of 5-HTT, in 70 CFS patients using PCR amplification of the blood genomic DNA, a significant increase of longer (L and XL) alleic variants was found in CFS patients ($p<0.05$). When we used the Selective Serotonin Reuptake Inhibitor for the treatment of 28 CFS patients, 1/3 of them recovered enough to return to work. Therefore, a serotonergic dysfunction might also be involved as one of the pathogenesis of CFS despite the patients not being in a depressed state.

Fig. 2 shows our current hypothesis of pathogenesis in CFS. The vast majority of trigger of CFS may be the increase of life stress. The genetic background including 5-HTT gene promoter polymorphism is also important to the susceptibility to the life stress. Under this condition, immune system dysfunction and/or abnormal regulation of the hypothalamo-pituitary adrenal axis might be occurred. In addition, low NK acitivity may be lead to the reactivation of herpes virus and/or chronic infection of rickettsias; causing the abnormalities of cytokines production (TGF-β, IFN, TNF, IL-1, IL-4, etc.). The most of symptoms found in CFS might be explained by the brain dysfunction caused by the abnormalities of cytokines. It is known that TGF-β suppresses the sulfokinase activity, and hence, the levels of DHEA-S are decreased. Recently, it was reported that acetylcarnitine transferase activity is proportional to the levels of DHEA-S, and so low levels of DHEA-S are related to the acylcarnitine deficiency found in CFS. Acylcarnitine dysbolism might

cause the decrease of biosynthesis of glutamate, and this abnormality is one of the key to understanding the chronic fatigue sensation in CFS.

The other pathway might be related to interferon. We used interferon for the treatment of patients with malignancy. At that time, these patients frequently complained of general fatigue, myalgia, althralgia and depression. Therefore, the interferon is thought to be involved in the signs and symptoms of CFS. It is well known that the levels of 2-5 oligoadenylate synthetase was elevated in the vast majority of patients with CFS, and recently the increase of abnormal RNase L was found in the patients with CFS. RNase L has not only an important effect on suppressing the viral growth under the production of the interferon when the patients have a viral infection, but also the undesirable effect on the serotonergic or dopaminergic neuron in the brain, resulting in prolonged general fatigue and depression. Other cytokines, TNF, IL-2 are also thought to be involved in the pathogenesis of chronic fatigue, and these studies are in progress.