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Preface

Molecular and Neuronal Mechanisms of Chronic Fatigue Syndrome: From Bench to Bedside

Fatigue is one of the symptoms produced by our bio-alarm system. However, we may not have paid enough attention to the importance of fatigue, since fatigue normally disappears after rest or sleeping overnight. It has been recognized that patients with chronic fatigue syndrome (CFS), showing debilitating and long-lasting fatigue which is not relieved by rest, has been producing a huge amount of economic loss in our modern society. The CFS is characterized by not only severe fatigue, but also the impairment of neuroendocrine, autonomic, cognitive and immune functions, suggesting a diturbance in the neuronal-endocrine-immune interactions. One of the reasons for not having a specific medicine may be because of the unknown etiology of this syndrome. Clinical symptoms have suggested an association of viral infection with the cause of CFS. Although researchers have not identified the specific pathogen yet, many possible viruses have been reported to induce CFS.

In this special issue co-organized by Dr. Yosky Kataoka (RIKEN, Kobe, Japan) and me, we present recent findings on molecular and neuronal mechanisms of CFS using animal models and human patients.

It is well known that chronic stress is deeply associated with the onset or exacerbation of CFS. Ogawa et al. demonstrated that rats given a sleep-depriving continuous stress showed morphologically atrophic and functionally suppressed somatotrophs as well as hyperactive melanotrophs including secretion of α-MSH (see the chapter by Ogawa et al.). They also suggested that the serum level of α-MSH can be a bio-marker for CFS at the early stage. Transforming growth factor-β (TGF-β) was also suggested as a possible bio-marker for CFS. TGF-β was identified from cerebrospinal fluid in physically exhausted rats, which was found to induce fatigue when administered to normal rats. Those findings in the animal models have been supported by the clinical study showing an elevation of active TGF-β in the serum of CFS patients (see the chapter by Inoue).

Neuroinflammation is characterized by activation of glial cells secreting cytokines, chemokines, radicals, growth factors and proteases in the central nervous system (CNS). It has been indicated that neuroinflammation plays an important role in various neurodegenerative diseases such as Parkinson's and Alzheimer's diseases and it is likely that CFS also involves neuroinflammation. Kataoka et al. showed presence of neuroinflammation using positron emission tomography (PET) during central fatigue, which was induced by excessive stimulation with cortical spreading depression of the brain. They also demonstrated that central fatigue induced by systemic injection of synthetic double-stranded RNA, polyriboinosinic:polyribocytidylic acid (poly I:C), was suppressed by minocycline (an inhibitor of microglial activation). In this immunologically induced fatigue model, it is suggested that the balance of interleuikin-1β (IL-1β) and its intrinsic antagonist, IL-1 receptor antagonist, is important for the induction and prolongation of fatigue (see the chapter by Kataoka et al.). Ifuku et al. also demonstrated that the activation of microglia in the hypothalamus, which was evoked by systemic poly I:C injection and was accompanied by the enhanced expression of microglial IL-1β, was involved in the onset of the immunologically induced fatigue (see the chapter by Ifuku et al.).

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In the clinical study, the impaired immune functions in the patients with CFS have been reported, although those are conflicting and inconsistent. Bradley et al. have noted that not only the decrease in natural killer cell activity, but also the dysfunction of T cells and B cells are associated with the CFS. They especially proposed the inefficient elimination of autoreactive B cells, which would lead to a non-inflammatory quiet autoimmunity affecting the CNS and immune system in CFS (see the chapter by Bradley et al.).

There are several evidences for the circadian rhythm disruption in CFS. Bonsall et al. have suggested that a decrease in the amplitude of circadian drive may play important role in maintaining CFS through the actions of cytokines in the suprachiasmatic nucleus, which is a master circadian pacemaker in the brain (see the chapter by Bonsall). Another consistent symptom of CFS is the blunt responsiveness of the hypothalamo-pituitary-adrenal axis, including glucocorticoid resistance and disruption of the diurnal cortisol pattern. They further referred to epigenetic modulation of glucocorticoid receptor (GR) mRNA encoding by histone deacetylases, suggesting that the decrease in GR expression would manifest as dysregulation of cortisol resulting in increased levels of fatigue (see the chapter by Sorenson).

Yamaguti et al. have studied from a large group of CFS patients (more than 1,000) about autonomic dysfunction. They demonstrated a sympathetic predominance evidenced by a significant increase in the ratio of Log LF (logarithmic low-frequency power/HF (high-frequency power) of the heart rate variability analysis even during sleep. They also found that the dysfunction of the parasympathetic nervous is involved in the pathophysiology of CFS patients with severe fatigue. Furthermore, the maximal Lyapunov exponent (MLE), which is considered to voids influence of non-stationary environments, such as social stress, is decreased in CFS, suggesting that a chaotic state in the autonomic nervous function has waned in CFS (see the chapter by Yamaguti).

Tanaka et al. have reviewed the data from behavioral, electrophysiological, and neuroimaging experiments related to the neural dysfunction in CFS. They propose that the facilitation system, which is a neural pathway or circuit to increase motor output from the motor cortex in order to compensate for the effects of acute physical fatigue. However, as subjects become acutely fatigued, the inhibition system, which limits the descending motor output during fatigue, is activated to avoid further fatigue. They suggested that repetitive and prolonged overwork and/or stress such as inflammation, oxidative stress, and energy deficiency could cause damage of the facilitation system and sensitization and/or classical conditioning of the inhibition system, resulting in a severe sustained fatigue sensation and functional disabilities (see the chapter by Tanaka).

It has been suggested that psychological factors such as childhood trauma and other negative life events are important risk factors for the onset, exacerbation, and/or relapse of CFS. Oka reported that a CFS patient showed a remarkable hyperthermic response to psychological stress (stress interview), although the patient demonstrated a bunted activation of the HPA axis. Further studies are necessary to determine how the hyperthermic responses are related to psychological stress-induced exacerbation of CFS symptoms (see the chapter by Oka).

This special issue highlights some of the recent topics in CFS research. We hope that this issue will help the researchers who have been studying CFS or the related disorders and will encourage the scientists in the different fields to be interested in the CFS, which shows a wide range of symptoms probably due to disorders in neural-endocrine-immune interactions with unknown etiology.

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