Fatigue Science for Human Health
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Preface and Mini-review: Fatigue Science for Human Health

Yasuyoshi Watanabe

What is fatigue? Why do we feel tired sometimes or seemingly all of the time? What is the physiological role or meaning of the sensation of fatigue? How is chronic fatigue related to various diseases? How can we prevent chronic fatigue and exhaustion?

In the past we really did not know very much about the mechanisms of fatigue. Fatigue or tiredness is really an important bio-alarm, without which we might drop into an unrecoverable exhaustive state and in the most severe case even die, referred to in Japanese as karoshi. As compared with the mechanisms of other bio-defense systems such as pain and fever, little is known regarding molecular/neuronal mechanisms of fatigue. Cytokine-prostaglandin systems are involved as the major factors in the induction and/or mediation of pain and fever. Although some pre-inflammatory cytokines may be the central mediator(s) in fatigue (see the chapters by Katafuchi and the one by Inoue et al.), the prostaglandin systems are probably not involved in the mechanisms of fatigue because cyclooxygenase inhibitors, both COX-1 and COX-2 ones, could not reduce the hypo-activity caused by poly I:C injection in rats, although they are quite effective as anti-febrile drugs (Matsumura K et al, unpublished data). Lactate, which was previously considered to be a candidate fatigue-inducing substance accumulating during severe exercise, is no longer thought to be a causative substance of fatigue (see the chapter by Tanaka and Watanabe).

Figure 1 shows the statistics on fatigue in Japan in 2004. Although surprisingly a lot of people are suffering from chronic fatigue lasting longer than 6 months (more than one-third of the Japanese population), integrated research on fatigue had not been organized until quite recently. Fatigue is a sensation that probably all people have experienced and is therefore quite familiar to all of us, but its molecular and neural mechanisms have not been elucidated yet, probably because of the complicated nature of the causes. However, we know that fatigue definitely
Are you tired?  
No (44%)  Yes (56%)

Period?  
<6 months (17%)  >6 months (39%)

Disturbance in daily life  
None (55%)  Yes (37%)  Often disturbed (7.4%)

Cause of chronic fatigue  
Overwork (42%)  Disease (19%)  Unknown (38%)

Fig. 1. Statistics in Japan in 2004. The research project under Ministry of Education, Culture, Sports, Science, and Technology, the Japanese Government made the questionnaire-based search with 2,742 answers from the citizens in Osaka area.

decreases the efficiency with which we perform our daily tasks or studies. Thus it is of great value to our modern society for scientists to extensively analyze the causes of fatigue and to develop methods to quantify fatigue, with the goal of developing methods or therapies to afford better recovery from and perhaps even avoidance of severe chronic fatigue. The economic gain would be really quite large if chronic fatigue could somehow be cured. To our regret and surprise, almost all commercially available means for recovery from fatigue are not yet based upon scientific and medical evidence.

In light of the situation outlined above, Watanabe and Kuratsune organized an integrated research project entitled “The molecular/neural mechanisms of fatigue and fatigue sensation and the way to overcome chronic fatigue” under the aegis of the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and carried it out from 1999 to 2005. The project was conducted by 26 laboratories in various universities and institutions with Yasuyoshi Watanabe as the chief researcher. The project made the following major contributions to our knowledge of fatigue: 1) Elucidation of the brain regions and their neurotransmitter systems responsible for fatigue sensation and chronic fatigue; 2) development of a variety of methods and scales to quantitatively evaluate the extent of fatigue; 3) development of animal models based on different causes of fatigue; 4) elucidation of molecular/neural mechanisms of fatigue in humans and animals; and 5) invention of various methods or therapies to treat chronic fatigue and chronic fatigue syndrome (CFS).

As can be seen in several chapters of this book, the pathogenesis of CFS is becoming a little clearer than before through the cooperation and findings of many investigators internationally from such fields as virology, immunology, endocrinology, physiology, biochemistry, psychiatry, and neuroscience.
In order to develop the foods and drugs to help overcome fatigue, we have been making efforts through the anti-fatigue project, organized by Soiken Co., Ltd., (2003–2007)(see the chapter by Kajimoto), and through the 21st Century COE Program called the “Establishment of the center of excellence (COE) to overcome fatigue (2004–2009).” More recently, the research has been directed not only toward foods and drugs to overcome fatigue but also toward various aspects of the environment, such as air-conditioning; the interior design of homes, hotel rooms, and offices; aromas; music; city design; and vehicular traffic. Although fatigue is a problem of individuals, it is also one of civilized societies, and we should therefore investigate and analyze the social aspects of fatigue, especially in terms of modern city life (see the chapter by Evengård). The contents of this book summarize our fatigue researchers’ achievements, and present the status of research on fatigue and the perspectives on remedies for chronic fatigue and chronic fatigue syndrome. To generate international discussion, we organized The International Conference on Fatigue Science—the first in 2002 in Sandhamn, Sweden, and a second in 2005 in Karuizawa, Japan. As a consequence, the editors and contributors decided to collect the papers presented at these two conferences and incorporate them in this book entitled Fatigue Science for Human Health.

Concerning the molecular mechanisms of chronic severe fatigue addressed in this book, the only ones clearly involved are the following:

1. Oxidative stress: its prolongation or poor elimination
2. Pro-inflammatory cytokines: their central role in fatigue mediation
3. Less energy reservoir state, especially for repair of damaged intracellular and intercellular components (e.g. carbonyl proteins)
4. Neuro-immune-endocrine dysfunction and characteristic autonomic nerve dysfunction

In this context, some possible bio-toxins and lowered detoxification capacities are highlighted.

Recent progress in the neuroscience field has been marked (see also the chapter by Natelson and the one by Chaudhuri et al). Particularly, I would like to introduce our hypothesis on brain dysfunction in chronic fatigue. The team with Watanabe and Kuratsu have investigated the brain regions responsible for the fatigue sensation by using positron emission tomography (PET), and found the regions in Brodmann’s area 10/11 well correlated with the fatigue sensation, areas in which motivation and evaluation of perceived information are organized (Tajima, S. et al., manuscript in preparation). Recent single-photon emission computed tomography (SPECT) studies [1–3] using 99mTc-hexamethyl-propylene-amine oxime revealed that most CFS patients showed cerebral hypoperfusion in a variety of brain regions such as the frontal, temporal, parietal, and occipital cortices; anterior cingulate; basal ganglia; and brain stem. Furthermore, they suggested that central nervous system (CNS) dysfunction may be related to the neuropsychiatric symptoms of CFS patients. To confirm these findings, we studied the regional cerebral blood flow (rCBF) in 8 CFS patients and 8 age- and sex-matched controls by use of 15O-labeled water (H₂¹⁵O) and PET, and found that the rCBF was lower in the CFS patient.
group than in the control group in the brain regions including the frontal, temporal, and occipital cortices; anterior cingulate; basal ganglia; and brain stem [4]. These brain regions correspond to various neuropsychiatric complaints: autonomic imbalance, sleep disturbance, many kinds of pain, and the loss of concentration, thinking, motivation, and short-term memory. Therefore, our results from the first quantitative rCBF study done on CFS patients with PET are in good agreement with the data from the previous SPECT studies, and indicate that various neuropsychiatric complaints found in CFS patients might be related to dysfunction in these regions of the CNS.

Furthermore, when we studied the cerebral uptake of [2-11C] acetyl-L-carnitine in the same 8 CFS patients and 8 age- and sex-matched normal controls by using PET, a significant decrease in uptake was found in several brain regions of the patient group, namely, in the prefrontal (Brodmann’s area 9/46d) and temporal (BA21 and 41) cortices, anterior cingulate (BA24 and 33), and cerebellum [4]. These findings suggest that the levels of neurotransmitters biosynthesized through acetyl-L-carnitine may be reduced in some brain regions of chronic fatigue patients and that this abnormality may be one of the keys to unveil the mechanisms underlying chronic fatigue sensation.

More recently, using magnetic resonance imaging (MRI), we found that patients with CFS have reduced gray matter (GM) volume in their bilateral prefrontal cortices. Furthermore, right-hemisphere GM volume correlated negatively with the subjects’ fatigue ratings [5]. This is consistent with the above-mentioned result that showed decreased uptake of acetyl-L-carnitine, perhaps indicating a decrease in the biosynthesis of glutamate, in the prefrontal cortex. The prefrontal cortex may therefore be part of the neural underpinnings of fatigue.

Much more striking, we demonstrated by functional MRI studies the vulnerability of the neuronal activity in task-unrelated brain regions in CFS patients, although in the healthy subjects decreased neuronal activity was seen only in task-related brain regions [6]. Apparently, a system guarding against further exhaustion may be built into the brain.

We also studied 5-HT transporter (5-HTT) density in 10 patients with CFS and 10 age-matched normal controls by using PET with the radiotracer [11C](+)-McN5652. Analysis using a statistical parametric mapping software (SPM99; The Wellcome Department of Cognitive Neurology, London, UK) revealed that the density of 5-HTTs in the rostral subdivision of the anterior cingulate was significantly reduced in CFS patients [7]. In addition, the density of 5-HTTs in the dorsal anterior cingulate was negatively correlated with the pain score [7]. Therefore, an alteration in the serotonergic neurons in the anterior cingulate plays a key role in the pathophysiology of CFS.

Apparently, these PET results on 5-HTT density seem to be inconsistent with our results regarding the 5-HTT gene promoter polymorphism [8], where CFS patients could have a greater frequency of the L allele, which affords greater transporter efficiency. However, it might be the case that the reduction in 5-HTT density in CFS patients with L and XL allelic variants is less than that in CFS patients with S allelic variants. Because 5-HT biosynthesis in the brain is thought to deteriorate
in patients with CFS, 5-HT deficiency in the synapses might be more serious in patients with L and XL allelic variants. If so, it is consistent with the finding that selective serotonin re-uptake inhibitor (SSRI) treatment is effective for some patients with CFS. To clarify the full particulars of brain dysfunction in patients with CFS, we are now studying 5-hydroxy-L-tryptophan (5-HTP) uptake, L-DOPA uptake, and muscarinic acetylcholine receptor density by using PET. We plan to report the results of these studies concerning brain dysfunction found in patients with CFS in the near future. So far, however, we propose the working hypothesis on this dysfunction in chronic fatigue, as shown in Fig. 2.

Quantification of fatigue or invention of fatigue scales specific for the induced load (physical load, mental load, or mixed ones) is also a central issue to be developed in fatigue science (Lists 1 and 2; see also the chapter by Kajimoto and the one by Kondo). For this purpose, we developed a new clinical scale based on the results of a 64-item questionnaire (see the chapter by Fukuda et al.). Also, non-verbal scales to assess frontal lobe function (see the chapter by Mizuno et al.), behavior amount (by using an actigraph), and autonomic function (by using acceleration plethysmography) have been developed. Blood and saliva samples from CFS patients and from individuals with induced fatigue (physical and mental) were analyzed, and we found a specific pattern or spectrum of the components [9]. By using these physiological and biochemical (including immunological and viral) biomarkers (see the chapter by Kajimoto), we started a project to develop evidence-based anti-fatigue foods, especially those foods that can prevent fatigue (Soiken
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List 1. Evaluation protocol for the extent of fatigue

**Questionnaire, VAS, Face scale**
- fatigue, sleep, life trends, temperament and character investment (TCI), food intake

**Physiological biomarkers**
- autonomic, cognitive, sleep diagram, activity, working memory, fatigability

**Biochemical biomarkers**
- virological, immunological, endocrinological, energy substrates, redox

**Doctor interview**
- motivation, vividness?

List 2. Scales/Biomarkers for quantification of fatigue

- **Cortical function: attention, concentration, and working memory**
  - Advanced Trail Making Test (ATMT)
  - Dual Task Test (DTT), n-back task
- **Evaluation by behavioral measures**
  - motion capture, actigraph (gyroscope-type)
- **Autonomic nerve function**
  - acceleration plethysmography (APG), ECG
- **Biochemical markers in the plasma and saliva**
  - immune and endocrine biomarkers, amino acids, iron, heme, vitamins, viruses and near infrared-factors

Project). In 2007, or by the beginning of 2008, we could have the first anti-fatigue product derived from the Soiken Project.

One thing is very clear: if we would like to elucidate the mechanisms of CFS and to devise a systematic remedy for CFS patients, we may learn more by studying both CFS and chronic fatigue. What is specific to CFS? Unfortunately, most studies have merely focused on the differences between CFS patients and healthy volunteers. However, whether factors or treatments relate to CFS or chronic fatigue is at times unclear and leads to confusion. If we could have some means of distinguishing between chronic fatigue and CFS, e.g., as like pre-disease and disease, respectively, we would be able to study at least three conditions (groups), i.e., healthy, chronic fatigue, and CFS. Elsewhere, we should compare healthy, CFS, and chronic fatigue with regard to other causes and diseases. Such studies could help both CFS and chronic fatigue patients. Toward this end, we propose here the promotion of “fatigue science for the benefit of human health.” It is our hope that more researchers from various disciplines will join the study of fatigue science after having read this book and the references cited therein.
On behalf of the editors, I would like to thank all the contributors to this book, and also all of their colleagues and collaborators. Some of them could not be included in this book because of a conflict of interest with original papers. I also thank Prof. Osamu Hayaishi, Prof. Hiroo Imura, the late Prof. Yasutomi Nishizuka, Prof. Ryoji Noyori, Dr. Teruhisa Noguchi, Prof. Teruo Kitani, Prof. Yutaka Oomura, and Prof. Nobuya Hashimoto, for their pertinent advice. In addition, many thanks are due to the members and staff of the research project “The molecular/neural mechanisms of fatigue and fatigue sensation and the way to overcome chronic fatigue” under the auspices of the Ministry of Education, Culture, Sports, Science, and Technology, Japan, and also to those of the 21st Century COE Program “Establishment of the center of excellence (COE) to Overcome Fatigue.” Finally, I am especially grateful to Dr. Junichi Seki, the Mayor of Osaka City; Prof. Satoru Kaneko, the President of Osaka City University (OCU); Prof. Yoshiki Nishizawa, the Dean of OCU Medical School; the members and colleagues of the anti-fatigue project organized by Soiken Co., Ltd.; Dr. Larry D. Frye for editorial help with this manuscript; and the editorial staff of Springer Japan for the great effort they made for the publication of this book.

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