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Editorial

Fatigue in the Central Nervous System

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Editorial

Definitions of fatigue and fatigue sensation given by the Japanese Society of Fatigue Science are as follows: "Fatigue is defined as a decline in the ability and efficiency of mental and/or physical activities that is caused by excessive mental or physical activities or disease. Fatigue is often accompanied by a peculiar sense of discomfort, a desire to rest, and a decline in motivation, referred to as fatigue sensation" [1]. Behavioral, electrophysiological, and neuroimaging studies using techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and magnetoencephalography (MEG) have recently clarified some of the neural mechanisms underlying human acute physical fatigue [2], acute mental fatigue [3], chronic fatigue [4], and fatigue associated with human diseases and syndromes [5].

As for acute physical fatigue, when we perform a physical task and the active muscle fibers become fatigued, an increase in voluntary effort is required to increase the motor output from the primary motor cortex (M1), to compensate for the physical fatigue and maintain physical performance [6-8]. This continues until the task requires a maximal voluntary effort. The system that increases the motor output from M1 is known as the facilitation system, and is composed of a re-entrant neural circuit that interconnects the limbic system, basal ganglia (BG), thalamus (TH), orbitofrontal cortex (OFC), dorsolateral prefrontal cortex (DLPFC), anterior cingulate cortex (ACC), premotor area (PM), supplementary motor area (SMA), and M1 [9-16]. Motivational input to this physical facilitation system enhances activity in the SMA and then the M1, thereby increasing motor output to the peripheral system [17]. In contrast, sensory input from the peripheral system to M1 during physical fatigue decreases motor output [18-23]. An inhibition system increases inhibitory input to M1 to limit the recruitment of motor units and/or slow the firing rate of active motor units in the M1 [8]. This physical inhibition system comprises a neural pathway that interconnects the spinal cord, TH, secondary somatosensory cortex, insular cortex (IC), posterior cingulate cortex (PCC), ACC, PM, SMA, and M1 [2]. The motor output from M1 is primarily regulated by the balance between these physical facilitation and inhibition systems [2].

As for acute mental fatigue, a conceptual model related to cognitive task performance has been proposed as a "dual regulation system" [3]. In this model, mental workload activates the mental facilitation system to maintain cognitive task performance in the presence of mental fatigue. The thalamic-frontal loop that interconnects the limbic system, BG, TH, and FC constitutes the mental facilitation system, and an increase in motivational input to this system increases its activation. However, mental workload also activates the mental inhibition system to impair cognitive task performance. The IC and PCC are involved in the mental inhibition system [24-28]. Acute mental workload activates the mental facilitation and inhibition systems, resulting in acute mental fatigue. Activation of the mental facilitation system maintains or improves cognitive task performance, whereas activation of the mental inhibition system impairs cognitive task performance. The balance between activation of these two systems determines whether performance of the cognitive task is impaired, maintained, or improved. Cognitive task performance is therefore regulated by these two systems through the dual regulation system.

Enhancement of the physical or mental facilitation system through psychological, behavioral, or physical triggers may have favorable effects against acute fatigue and improve performance. However, excessive enhancement of the facilitation system at the expense of functions may cause dysfunction of the system and lead to further fatigue. Dysfunctions of the facilitation system lead to difficulties in driving the system. Motivation or voluntary effort enhances the facilitation system, whereas further enhancement of the facilitation system causes further dysfunction of the system [29-31]. This may induce chronic or accumulated fatigue [4]. Chronic fatigue has therefore been proposed to occur due to a failure in the facilitation system. In fact, people with chronic fatigue show dysfunction of the facilitation system during motor imagery task trials [29], as well as during cognitive task trials [32,33], possible resulting from metabolic, functional, and structural damage to the BG [34], OFC [35], PFC [35,36], and ACC [35], all of which are part of the facilitation system. Enhanced activation of the physical or mental inhibition system may be centrally sensitized and classically conditioned by repetitive and prolonged overwork and/or stress, because central sensitization and classical conditioning of the inhibition system has been successfully achieved in humans [37], and an animal model of fatigue was established using central sensitization and classical conditioning methods [38]. Central sensitization and classical conditioning of the inhibition system are considered to play important roles in the development of severe and long-lasting fatigue, particularly chronic fatigue [4]. Such excessive response of the inhibition system may be closely associated with the pathophysiology of chronic fatigue [4].

In human diseases or syndromes such as multiple sclerosis and chronic fatigue syndrome (CFS), several studies have shown dysfunction and/or abnormal activation patterns in the brain regions involved in the facilitation and inhibition systems [39-43]. Dysfunction of the facilitation system and enhancement of the inhibition system both result in difficulties driving the facilitation

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system. Voluntary effort enhances the facilitation and inhibition systems, but the enhanced inhibition system causes further difficulties in driving the facilitation system [44-47]. This process induces dysfunction of the facilitation system and activation of the inhibition system through central sensitization or classical conditioning of the inhibition system, which we describe later, and causes severe fatigue in these diseases and syndromes [5].

In this letter, we describe mechanisms of fatigue in the central nervous system, mainly focusing on the existence of the facilitation and inhibition systems. In the future, we aim to conduct multifaceted studies to construct a comprehensive view of the neural mechanisms underlying fatigue and the strategies employed to overcome fatigue.

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