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Research report

Tryptophan circuit in fatigue: From blood to brain and cognition

Masatoshi Yamashita [a,*], Takanobu Yamamoto [b]

[a] Department of Neuroscience, Psychology and Behaviour, University of Leicester, Lancaster Road, Leicester LE1 9HN, United Kingdom
[b] Department of Psychology, Tezukayama University, 3-1-3, Gakuenminami, Nara-shi, Nara 631-8585, Japan

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ABSTRACT

Brain tryptophan and its neuroactive metabolites play key roles in central fatigue. However, previous brain function analysis targets may have included both glia and neurons together. Here, we clarified the fatigue-cognitive circuit of the central-peripheral linkage, including the role of glial-neuronal interaction in cognition. Using a rat model of central fatigue induced by chronic sleep disorder (CFSD), we isolated presynaptic terminals and oligodendrocytes. Results showed that compared to control group, presynaptic levels of tryptophan, kynurenine, and kynurenic acid, but not serotonin, in the CFSD group were higher in the hypothalamus and hippocampus. Moreover, CFSD group had higher oligodendrocytic levels of tryptophan, and impaired spatial cognitive memory accuracy and increased hyperactivity and impulsivity. These findings suggest that dynamic change in glial-neuronal interactions within the hypothalamus-hippocampal circuit causes central fatigue, and increased tryptophan-kynurenic acid pathway activity in this circuit causes reduced cognitive function. Additionally, CFSD group had 1.5 times higher plasma levels of tryptophan and kynurenine. Furthermore, in rats undergoing intraperitoneal administration of kynurenine (100 mg/kg) versus vehicle, kynurenine-treated rats showed enhanced production of kynurenic acid in the hippocampus, with suppressed recall of retained spatial cognitive memory. The study revealed that uptake of periphery-derived kynurenine and tryptophan into the brain enhances kynurenic acid production in the brain, and the three factors produce amplification effect involved in the role of central-peripheral linkage in central fatigue, triggering cognitive dysfunction.

1. Introduction

Central fatigue, known as mental fatigue in humans, is implicated in pathological fatigue condition of chronic fatigue syndrome (Castell et al., 1999), and leads to reduced mental task performance, disrupted social life, and impaired brain functions. Central fatigue that is induced by chronic sleep disorder reportedly affects 40% to 80% of school refusal children (Farmer et al., 2004; Miike, 2009), causing them difficulty in returning to school (Tomoda et al., 1994; Tomoda et al., 1997), development of psychiatric disease (Farmer et al., 2004; Miike, 2009), and brain dysfunction (Tomoda et al., 2000).

Conventional studies on central fatigue have supported the 'serotonin hypothesis,' in which tryptophan uptake into the brain enhances serotonin production, thereby suppressing treadmill performance in the rat model of post-exercise fatigue (Acworth et al., 1986; Cermak et al., 2012; Melancon et al., 2012; Newsholme and Blomstrand, 2006). The hypothesis was also supported by an elevation in blood tryptophan level concentration during postoperative fatigue in humans (Yamamoto et al., 1997). However, since tryptophan taken up into the brain has two metabolic pathways, serotonin pathway and kynurenine pathway, which account for 5% and 95% of tryptophan metabolism, respectively (Schwarcz and Pellicciari, 2002), possible involvement of the tryptophan-kynurenine pathway in the mechanism of central fatigue induction has been pointed out. Meanwhile, 40% of kynurenine in the brain is produced in the central nervous system, whereas 60% has its origin in the peripheral nervous system (Gal and Sherman, 1978; Wu et al., 2013). Rapid passage of kynurenine across the blood-brain barrier has also been reported (Gal and Sherman, 1978; Wu et al., 2013). Kynurenine is also metabolized via two metabolic pathways, with the first step involving catalytic reaction with kynurenine aminotransferase localized in astrocytes, resulting in production of kynurenic acid (Schwarcz et al., 2012). Furthermore, there is some evidence that may explain the mechanism of central fatigue induction, including reduced spontaneous motor activity and memory performance in rats receiving kynurenic acid administration (Yamamoto et al., 2012), and elevated concentrations of tryptophan and kynurenic acid in the brain in sleep deprivation-induced fatigue (Yamashita and Yamamoto, 2014).

* Corresponding author.
E-mail addresses: myamashita.fatiguepsychology@gmail.com (M. Yamashita), takaoxford@gmail.com (T. Yamamoto).

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However, given that neurons make up only 10% of the brain cells, compared with 90% made up by glial cells (Allen and Barres, 2009), conventional brain function analysis targets may include both glial cells and neurons. For example, oligodendrocytes, a type of glia, protect neural axons by forming a myelin sheath around the axons to allow saltatory conduction of nerve action potentials (Barres and Raff, 1999). Furthermore, oligodendrocytes are involved in regulation of kynurenic acid production in the brain, with dependence on the concentration of tryptophan transported by the system L-transporter (Wejksza et al., 2005). Thus, the results of conventional studies on central fatigue do not provide clear evidence that the central fatigue induction mechanism is attributable to the characteristics of the central-peripheral linkage, including the role of glial-neuronal interaction mechanism. That is, how tryptophan and kynurenine present in the periphery behave to induce central fatigue in the glia-neuron circuit remains unknown. Furthermore, the dynamics of passage of monoamines and their metabolites between glial cells and neurons during central fatigue have yet to be elucidated. The basic findings from the present study have promise of offering novel insight into the central/mental fatigue status induced by chronic sleep disorder common among school refusal children. Thus, the present study may greatly contribute to elucidating latent mental problems in society from a scientific perspective.

In Experiment 1, we investigated the relationship between the change in intracerebral dynamics of kynurenic acid and acquisition and recall processes of spatial cognitive memory, using rats undergoing behavioral pharmacological manipulation of kynurenine. In Experiment 2, this rat model of central fatigue induced by chronic sleep disorder (CFSD) was also used to observe any changes in the peripheral dynamics of tryptophan and kynurenine. Furthermore, the changes in the dynamics of tryptophan and monoamine and their metabolites in oligodendrocytes and synaptosomes (presynapse) of neurons were observed to investigate their relationship with cognitive function.

2. Results

2.1. Experiment 1

2.1.1. Training test on the Morris water maze task

Escape latency for the Morris water maze is provided in Fig. 1B. A two-way ANOVA of group (vehicle and L-kynurenine) and training period (Days 1–12) showed a significant main effect of training period ($F_{(10,\ 80)} = 8.50$, $P < 0.001$). Multiple comparison using Bonferroni test revealed that, compared with training period days 8–12, training period day 1 significantly prolonged escape latency. This result showed the acquisition of spatial cognitive memory in both groups.

2.1.2. Probe test on the Morris water maze task

In the probe test, since there was no significant difference in memory acquisition performance between groups, administration

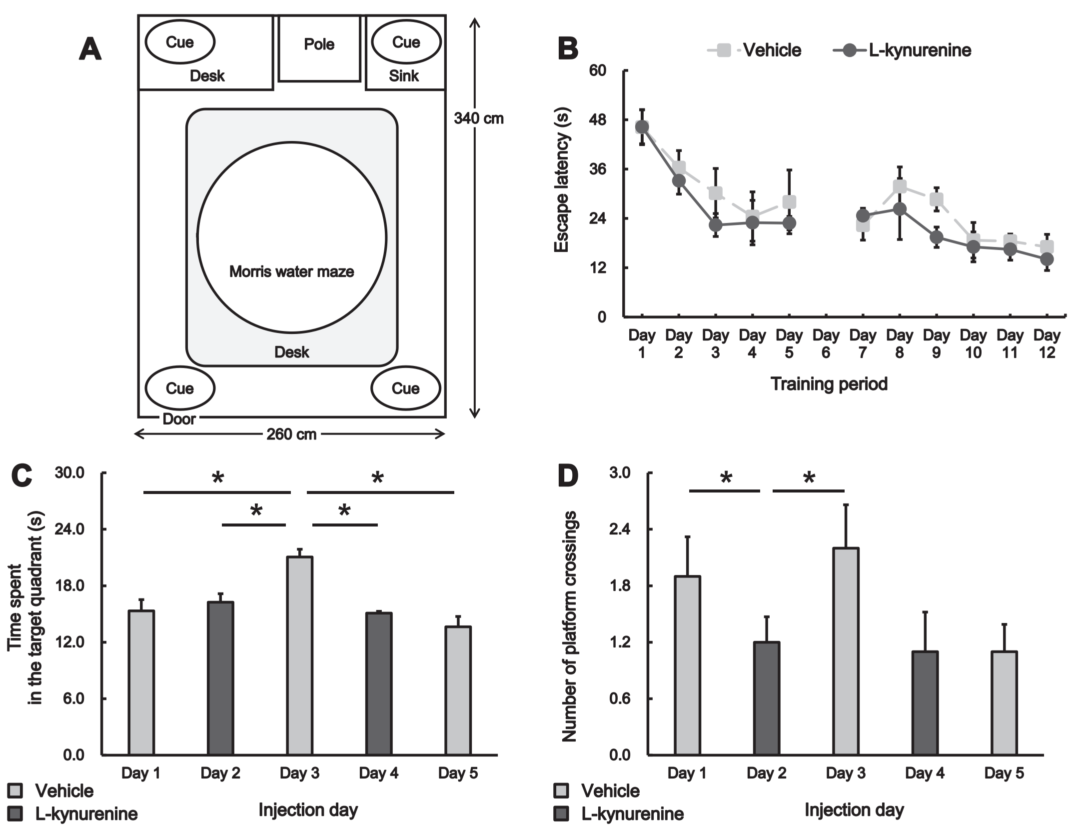

Fig. 1. Effect of chronic intraperitoneal administration of L-kynurenine for Morris water maze. (A): A schematic diagram of the top view of pool and visual spatial cues in the laboratory. (B): Escape latency during training period was defined as spatial cognitive memory acquisition training. Rats treated with L-kynurenine showed no significant difference in the level of spatial cognitive memory acquisition during training period (Days 1–12) compared to rats treated with vehicle. Parameters are expressed as mean ± SEM. n = 5 for each group. (C): Since there was no significant difference in memory acquisition between groups in the training test, the two groups (n = 5 each) were regrouped to one group (n = 10), and then administration of L-kynurenine or vehicle was alternately conducted on every other day. In the probe test, the time spent in the target quadrant was defined as the level of recall of retained spatial cognitive memory. The level of recall of retained spatial cognitive memory was shorter on Day 2 and Day 4, when L-kynurenine was administered, than on Day 3, when vehicle was administered. (D): In the probe test, number of platform crossings was used to define the accuracy of recall of retained spatial memory. Accurate recall of retained spatial cognitive memory on Day 2, when L-kynurenine was administered, was lower than on Day 1 and Day 3, when vehicle was administered. Parameters are expressed as mean ± SEM. *$P < 0.05$ vs. L-kynurenine or vehicle treatment. n = 10 for each treatment.