



# The relationship between central fatigue and Attention Deficit/Hyperactivity Disorder of the inattentive type

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## Abstract

Chronic fatigue and central fatigue with malaise significantly impair quality of life. Inattention caused by central fatigue is closely related to attention deficit/hyperactivity disorder (ADHD) symptoms, but the neurochemical mechanism of central fatigue remains hypothetical. The serotonin hypothesis of central fatigue was proposed first, serving as the central dogma for the molecular and neural mechanisms of central fatigue, and underpinning many studies. The tryptophan hypothesis was proposed because tryptophan released into the synaptic cleft of neurons in the brain coincides with and responds sensitively to development of fatigue. Tryptophan is highly bioactive, with brain concentrations of 50 to 200 times that of serotonin. The tryptophan-kynurenic acid-synergy hypothesis posits that central fatigue is not monocausal but a synergistic effect between tryptophan itself and its catabolite kynurenic acid. Central fatigue is associated with mental health problems and is a cause of inattention, thereby warranting scrutiny for its relationship with ADHD. Fatigability in ADHD is mediated by tryptophan, in which abnormal enhancement of the tryptophan-kynurenine-kynurenic acid pathway causes an imbalance in monoamine nervous system function. Notably, noradrenergic neuronal dysfunction is associated with the characteristic inattention of ADHD. Neutral amino acids such as branched-chain amino acids (BCAAs) can assist recovery from attentional and cognitive decline caused by central fatigue. Since they are transported by the same L-amino acid transporter as tryptophan, BCAAs compete with tryptophan to inhibit its brain uptake. Controlling central fatigue this way may improve attentional cognitive performance.

**Keywords** Central fatigue · ADHD · Tryptophan · Kynurenic acid · BCAAs · Monoamine

## Introduction

### Central (Mental) fatigue and ADHD

Feelings of ill-health and stress in modern life have grown ever more serious with the added weight of the COVID-19 pandemic, and mental health problems marked by mental fatigue (central fatigue) linked to tryptophan metabolism have become a global issue [1]. Fatigue has conventionally been seen as a physical phenomenon (muscle fatigue),

but with changes in the industrial structure of society and in people's lifestyles, attention is increasingly being paid to fatigue of the central nervous system. This concept of central fatigue was first proposed by Ikai et al. in the 1960s, and its origin is linked to the activity of the central nervous system, as for muscle fatigue [2]. The “fight-or-flight response” is a linkage between the mind and body in which the excitation of the central nervous system boosts muscle output. Initially, central fatigue was defined as “a decrease in the level of voluntary excitation,” but our findings have shown that it cannot be explained without taking into account the entire intracerebral area that is not associated with voluntary activity [3].

In the latter half of the 20th century, the concept of chronic fatigue syndrome (CFS) was proposed to describe a condition that causes long-lasting severe fatigue and tiredness of unknown origin [4]. Fatigue, as well as pain and fever, is one of the body's three major warning systems; a signal that cautions the brain to rest. In patients with CFS,

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overactivity of this signal is believed to cause generalized fatigue. The fatigue signal in humans with CFS [5] and in patients after surgery [6] is produced by a significant uptake of plasma tryptophan into the brain. Thus, the role of tryptophan in central fatigue is important not only in pathological conditions but also in physiological fatigue.

Furthermore, central fatigue appears to affect the severity and behavioral symptoms of neurodevelopmental disorders. Byun et al. (2013) [7] reported that patients with the inattentive type of adult attention deficit/hyperactivity disorder (ADHD) have poorer sleep quality and more severe central fatigue than those with the mixed type. Aarsland et al. (2015) [8] also reported that adults with ADHD have lower levels of tryptophan, kynurenine and kynurenic acid than healthy individuals, suggesting that tryptophan and kynurenine levels are correlated with the severity of current ADHD symptoms. Thus, the degree of central fatigue and associated changes in levels of tryptophan and its metabolites may intensify the severity and behavioral symptoms of ADHD. However, since the assessment of ADHD is determined by behavioral characteristics in children up to the age of 12, it is still unclear whether the results are similar to those for ADHD in adults.

This paper first describes the history of the advocacy of central fatigue, focuses on the susceptibility to fatigue in ADHD as a future outlook and outlines its relationship with inattention behavioral symptoms.

## The serotonin hypothesis of central fatigue

The first report to explain the mechanism of central fatigue from a biochemical standpoint was published in 1986 [9]: the so-called serotonin-enhancement hypothesis. In the fatigued state, free fatty acids in circulating blood increase, boosting their binding affinity to albumin and thereby increasing levels of albumin-bound free fatty acids. On the other hand, albumin also has the ability to bind free tryptophan, but under fatigued conditions, the binding tendency of albumin shifts toward free fatty acids, resulting in an increase in free tryptophan and promotion of its uptake into the brain. Since tryptophan is a precursor of serotonin, this process facilitates the synthesis of serotonin in the brain. The hypothesis is that elevated serotonin levels inhibit other neurons, resulting in central fatigue. One of the phenomena seen during central fatigue is the induction of drowsiness, and the serotonin molecule is known to be involved in sleep. Thus, the serotonin hypothesis has become the central dogma for considering the molecular and neural mechanisms of central fatigue, and on which many studies are based.

## The tryptophan hypothesis of central fatigue

As mentioned above, plasma free tryptophan levels are elevated in CFS and the postoperative fatigue state in humans. In addition, when tryptophan in plasma is taken up into the brain, it competes with other amino acids in the L-amino acid transporter (LAT) system at the blood-brain barrier [10], and since branched-chain amino acids (BCAAs) decrease during fatigue, the relative ratio of tryptophan increases, creating the conditions for uptake into the brain. However, the most critical point is how readily the tryptophan taken up into the brain can be synthesized into serotonin. We have examined the kinetics of tryptophan and serotonin after rats were run to fatigue and found that tryptophan increased significantly in all brain regions investigated, while serotonin was not significantly elevated in other regions of the brain (motor cortex, hypothalamus, hippocampus and thoracic spinal cord) except for the striatum [3] (Table 1). Given the elicitation of behavioral inhibition such as drowsiness and lethargy, and the results of electrophysiological experiments that show suppression of the firing of raphe nucleus neurons [11] when tryptophan is orally administered to humans, it is reasonable to conclude that tryptophan itself is bioactive. As the concentration of tryptophan in the brain is 50 to 200 times higher than that of serotonin, it is likely to be highly bioactive [12]. Furthermore, by observing the real time changes of tryptophan and serotonin released into the synaptic cleft by microdialysis, we found that striatal tryptophan responded rapidly to fatigue and continued to rise and then again responded rapidly in the recovery period from fatigue to return to baseline. Tryptophan was thus found to be extremely sensitive and specific to fatigue stimuli (Fig. 1). Furthermore, the release of tryptophan was significantly suppressed in the group that had received BCAAs beforehand. Serotonin, on the other hand, increased transiently in the early stages, but returned immediately to baseline regardless of the fatigue load and remained at that level thereafter. This indicates that serotonin is not specific to fatigue. More importantly, *in vitro* experiments using isolated synaptosomes (nerve endings) showed that when tryptophan was added, the nerve endings released large amounts of tryptophan. We are yet to ascertain the details of this mechanism, but it appears that recognition by tryptophan receptors further promotes the release of tryptophan into the synaptic cleft. Therefore, it appears that tryptophan may play a role as a neuromodulator rather than as a neurotransmitter. This interpretation, must also take into account the tryptophan transport system and the presence of receptors [12]. However, no serotonin release was observed in similar *in vitro* experiments. The findings in rats given a tryptophan-deficient diet, in which reduction

**Table 1** Serotonin precursor uptake to regional brain synaptosomes caused by running to fatigue in analbuminemic rats (pmol/mg protein)

	Tryptophan	5-hydroxy-tryptophan	5-HT	5-HIAA
<b>Striatum</b>				
Control	52 ± 4.85	0.83 ± 0.08	4.26 ± 0.23	6.14 ± 0.60
Fatigue	71 ± 2.07***	1.75 ± 0.17****	5.12 ± 0.19**	6.54 ± 0.39
<b>Motor cortex</b>				
Control	48 ± 3.90	0.50 ± 0.02**	3.4 ± 0.26	2.18 ± 0.25
Fatigue	62 ± 2.53**	0.96 ± 0.15	2.7 ± 0.51	2.50 ± 0.36
<b>Hypothalamus</b>				
Control	42 ± 1.12	0.29 ± 0.02	5.16 ± 0.28	9.49 ± 0.27
Fatigue	53 ± 4.36*	0.46 ± 0.06**	4.63 ± 0.46	9.52 ± 1.00
<b>Hippocampus</b>				
Control	34 ± 2.87	0.30 ± 0.04	1.59 ± 0.24	3.02 ± 0.27
Fatigue	54 ± 2.59****	0.61 ± 0.05****	1.40 ± 0.10	3.23 ± 0.22
<b>Thoracic cord</b>				
Control	24 ± 3.19	0.13 ± 0.02	6.21 ± 0.65	2.21 ± 0.31
Fatigue	32 ± 1.76*	0.20 ± 0.02*	3.24 ± 0.39***	2.00 ± 0.13

Mean ± s.e.m., n = 6. \*p < 0.05 \*\*p < 0.025 \*\*\*p < 0.005 \*\*\*\*p < 0.001; Control vs. Fatigue

5-HT: 5-hydroxytryptamine, 5-HIAA: 5-Hydroxyindoleacetic acid, s.e.m.: standard error of the mean

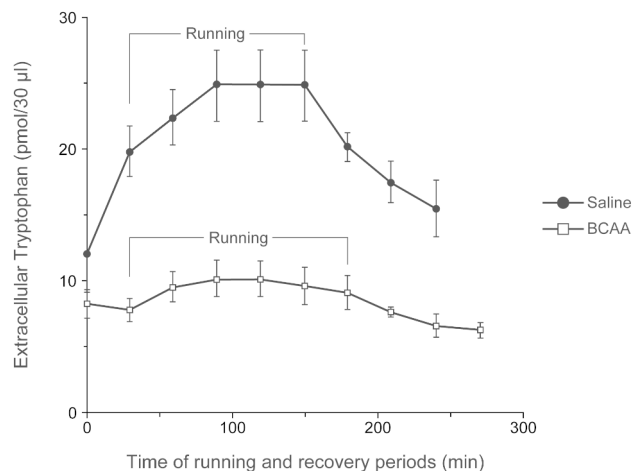
(Reused from Reference 3. Yamamoto T, Newsholme EA (2005). Fatigue Science, Ishiyaku Publishers, Inc., Tokyo, pp.35–41)

in brain tryptophan levels prolonged the time to exhaustion, further support the tryptophan hypothesis [13].

## Tryptophan-kynurenic acid synergy hypothesis of central fatigue

It is believed that increased tryptophan is normally metabolized to serotonin, but attention should more appropriately be paid to the synthesis of kynurenic acid [14]. 5% of the tryptophan taken up by the brain is used in the serotonin pathway, and the remainder—the majority, or 95%—is metabolized from kynurenine on the kynurenic acid pathway [15]. Hence, the kynurenine-kynurenic acid pathway also warrants scrutiny.

Previous studies have reported that tryptophan and kynurenic acid levels in the hippocampus and hypothalamus are higher in rats with central fatigue induced by sleep deprivation than in healthy rats, which are associated with suppression of spatial memory and social behavior [16, 17]. It is also known that tryptophan and kynurenine in the blood, which have an additive effect during central fatigue, are actively taken up into the brain [16]. Furthermore, when rats were administered kynurenine, a precursor of kynurenic acid, and made to perform spatial learning in

**Fig. 1** Extracellular tryptophan concentrations after administration of BCAAs or saline

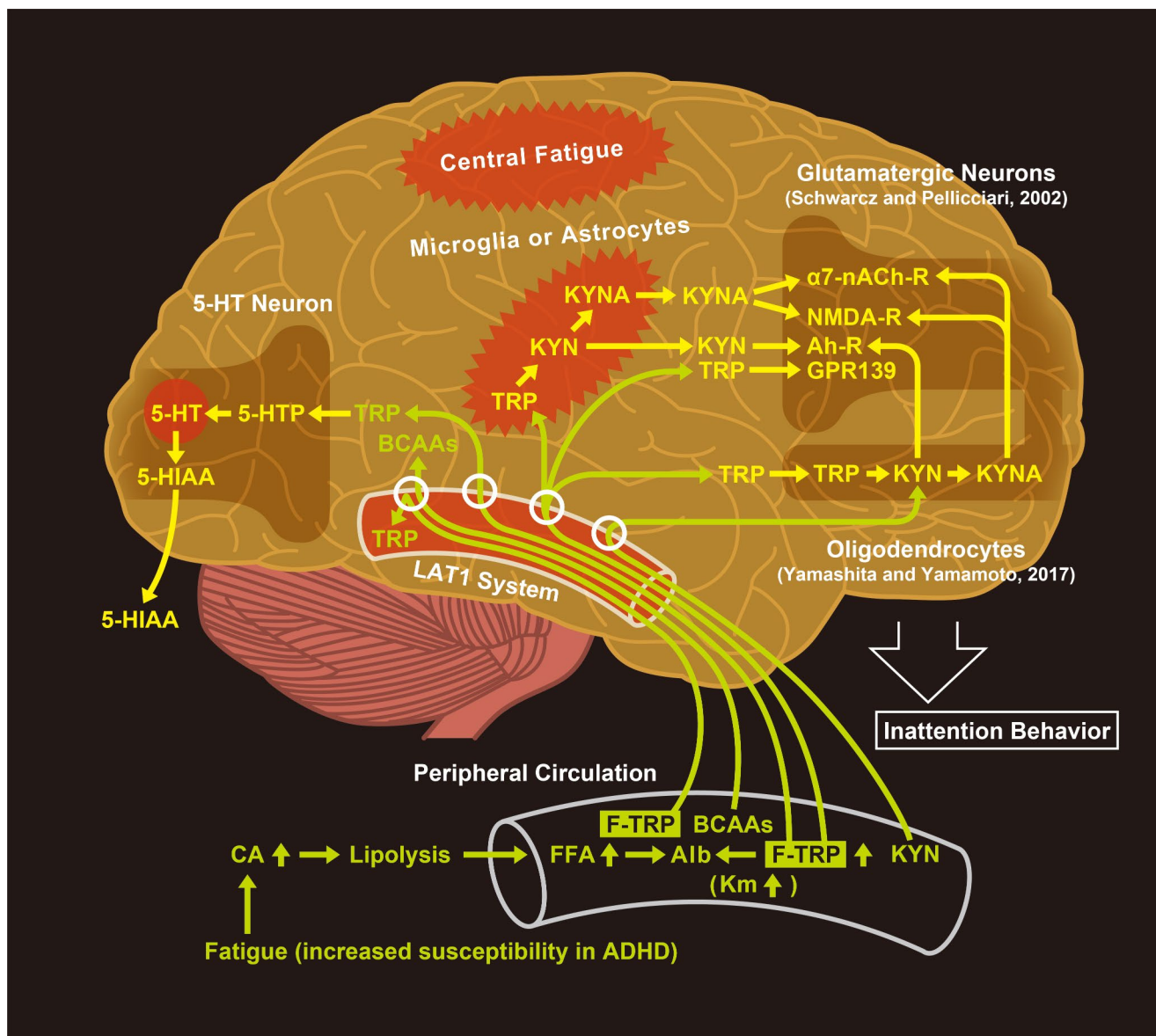
Mann-Whitney, U test:  $p < 0.0001$ , Saline ( $n = 45$ ), BCAAs ( $n = 40$ ). One-quarter of rats in the saline group (maximum, 156 min) and 4/5 of those in the BCAAs group (maximum, 240 min) ran for more than 150 min.

BCAAs: branched-chain amino acids. (Reprinted from Reference 12 with Permission. © The Canadian Journal of Neurological, published by Cambridge University Press.)

the Morris water maze, their performance was diminished [16]. Kynurenic acid levels in the brain were also sharply elevated in this experiment. Given that kynurenic acid is an antagonist of N-methyl-D-aspartate (NMDA) receptors or  $\alpha 7$  nicotinic receptors in the body [18], (Fig. 2), it is very likely to be implicated as a central fatigue substance. Furthermore, the majority of tryptophan is metabolized to kynurenic acid and quinolinic acid via the kynurenine pathway, suggesting that kynurenine metabolites play a key role in central fatigue. We found that, compared with saline-treated control rats, microinjection of 3 nmol kynurenic acid into the third ventricle reduced open field and rearing activity, and injection of 0.25 mM kynurenic acid increased running fatigue in a dose-dependent manner [12]. This suggests that the increased tryptophan and kynurenine metabolites in the peripheral and central regions are unquestionably the basis of central fatigue [14]. Interestingly, since tryptophan intake in healthy subjects is said to reduce activity in the frontal and parietal lobes and other areas during the Stroop task (a measure of attentional function) [19], it is at least possible that tryptophan and its metabolites are related to inattention.

## ADHD of the inattentive type and central fatigue

ADHD, as defined in the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [20], is a neurodevelopmental disorder characterized by inattention,



**Fig. 2** Involvement of central fatigue-based inattention behavior and TRP-KYNA synergistic action  
 Triggered by the presence of a fatigue-prone constitution in ADHD, the binding affinity of TRP to albumin decreases, and the level of F-TRP in plasma increases. Plasma F-TRP is taken up in the brain and metabolized to KYNA, and the synergistic action of TRP and KYNA causes central fatigue

It cannot be denied that tryptophan binds to orphan receptor and has activity as a neuromodulator. As a basis for this, there is a report [40] that GPR139 tryptophan receptor is expressed in the brain. Therefore, like amino acid neurotransmitters, tryptophan is no exception, and it is considered that it binds to GPR139 and induces the expression of ADHD-specific easy fatigue and inattention behavior. But most importantly, the development of central fatigue is most likely amplified and triggered by the synergistic action of tryptophan and its metabolite, kynurenic acid

In addition to the prefrontal glutamatergic neurons in Fig. 2, attention-related locus coeruleus-prefrontal noradrenergic neurons can be envisioned [41, 42]

F-TRP: free tryptophan, TRP: tryptophan, KYNA: kynurenic acid, KYN: kynurenine, 5-HT: serotonin (5-hydroxytryptamine), Alb: albumin, FFA: free fatty acid, CA: catecholamine, 5-HIAA: 5-hydroxyindoleacetic acid, 5-HTP: 5-hydroxytryptophan, LAT1: L-amino acid transporter, NMDA-R: n-methyl-d-aspartate-R, α7-nACh-R: α7-nicotinic acetylcholine-R, Ah-R: aryl hydrocarbon-R, GPR139: orphan GPR139 receptor, BCAAs: branched-chain amino acids

hyperactivity and impulsivity, and in my research I have specifically focused on the subtype in which inattention is the predominant feature. We have reported that central fatigue is related to the cause of symptoms of inattention in

ADHD [21]. Briefly, using the AASS scale instrument we conducted a questionnaire survey of human adults.

On the basis of assessment of 4 fatigue scale factors (mental fatigue, peripheral fatigue, sleep disorder and

depression), participants were divided into 4 groups: the inattention type, hyperactivity/impulsive type, mixed type and control groups. Mental fatigue scores were significantly higher in the inattention-type group than in the hyperactivity/impulsive type and control groups.

Furthermore, at the animal experiment level, the Nagase analbuminemic rat (NAR), a rat that is easily fatigued, has a reduced ability to inactivate tryptophan to 5-HIAA [12]. In addition, because the activity in the monoamine system required for attentional function is also reduced in this animal's prefrontal cortex, it has been proposed as an animal model of ADHD [22]. These facts suggest a relationship between central fatigue and attention-deficit ADHD.

Therefore, the characteristic susceptibility to fatigue seen in ADHD is caused by a tryptophan-related mechanism (Fig. 2). I have also pointed out that impulsivity and hyperactivity are common behaviors that tend to be observed in all neurodevelopmental and psychiatric disorders, including ADHD, but that ADHD is also characterized primarily by inattentive behavior. Tryptophan is involved in fatigue and mood swings, causing central fatigue [6, 23, 24]. Morgan and colleagues noted changes in tryptophan associated with attention, reporting that study participants taking tryptophan showed reduced activity in the central posterior gyrus, angular gyrus, inferior frontal gyrus, temporal gyrus and parietal lobe during the Stroop task [19]. This suggests that tryptophan levels in ADHD may be related to attention-based behavioral performance. Furthermore, it has been suggested that in adult ADHD patients, symptoms of inattention are more intensely expressed than those of hyperactivity and impulsivity [25]. With regard to central fatigue in ADHD, it has also been reported that adults with ADHD exhibit higher fatigue scores than healthy individuals and that patients with CFS exhibit ADHD symptoms more frequently than healthy individuals [26]. This suggests that ADHD is strongly associated with CFS and other manifestations of severe central fatigue.

Previously, we have noted that central fatigue can be explained by neurochemical mechanisms involving tryptophan and its metabolites [12]. Thus, as shown in Fig. 1, competitive inhibition with tryptophan by BCAAs at LAT indicates that recovery from central fatigue is possible.

## Recovery of cognitive ability from central fatigue

It is possible to restore cognitive ability from a state of central fatigue, the method of which is based on the serotonin or tryptophan hypotheses. In brief, if the trigger of central fatigue is serotonin or tryptophan, it is necessary to inhibit brain uptake of these substances that cause central fatigue.

When tryptophan enters the brain as a precursor of serotonin and kynurenine, it is transported by LAT at the blood-brain barrier. Branched-chain amino acids (BCAAs: valine, leucine and isoleucine) are also primarily transported across the blood-brain barrier (BBB) by members of the L-system amino acid transporter (LAT) family, mainly LAT1. LAT1 (SLC7A5, solute carrier family 7 amino acid transporter light chain, L system member 5) is preferentially expressed in the brain in the basolateral and apical membranes of endothelial cells of the BBB [27], so BCAAs compete with tryptophan.

Therefore, increasing the intake of BCAAs beforehand will hinder the entry of tryptophan into the brain, potentially preventing or eliciting recovery from fatigue. In fact, rats treated with BCAAs in advance show more than twice the anti-fatigue effect than those not treated [10]. Similarly, the same effect can be obtained using 2-aminobicyclo[2,2,1]heptane-2-carboxylic acid (BCH), a specific inhibitor of LAT, instead of BCAAs.

Hassmén et al. gave subjects a carbohydrate-only mixture containing BCAAs during a 30-km cross-country race, and had them perform a cognitive assessment test before and after the race. The participants who received BCAAs in advance improved their performance on the Stroop color-word test in the range of 3–7% ( $p < 0.05$ ). However, there was no difference in the pre- and post-race performance of the participants who were given a placebo. In addition, the performance of the BCAAs group remained unchanged for the shape-rotation and figure-identification tasks of the psychological test, as did the pre-race performance, but the placebo-treated participants performed worse on these tests (25%,  $p < 0.05$ ; 15%,  $p < 0.05$ , respectively) [28]. These psychological measures are essentially cognitive tests that require a person to correctly identify geometric shapes, check phrases, and perform mathematical calculations and short-term memory tasks within a set time frame. On the other hand, the cognitive performance of the BCAAs group after fatigue is not reflected in the results of the profile of mood states scale (POMS; depression, tension, anger, confusion, fatigue and vigor), and is not improved by administration of BCAAs, suggesting a mechanism other than the serotonin hypothesis for mood.

## Relationship between monoamine neural circuits and inattention in ADHD

Given the hypothesis for development of central fatigue based on tryptophan-kynurenic acid, several processes are required to reach the fatigue state. Both inattention in ADHD and CFS have been associated with decreased activity in the caudate nucleus [29, 30]. This suggests that

hypoactivity in the caudate nucleus is induced by enhancement of the kynurenine pathway and increased peripheral tryptophan, resulting in central fatigue in ADHD. Some reports suggest that the relationship between ADHD and central fatigue is due to an imbalance in the monoamine nervous system mediated by the serotonin and dopamine systems [22, 31–33]. This imbalance is linked to inhibition of the release from the dopamine and noradrenaline nervous system [31], further impairing the mutual regulation mechanism of the monoamine nervous system. It is also suggested that enhancements in both the serotonin pathway [32] and the kynurenine pathway [34] are involved in triggering the symptoms of inattention in ADHD. Thus, both the monoamine and kynurenine pathways are involved in the inhibition of dopamine and norepinephrine release, which may induce symptoms of inattention in ADHD. Also, Arnsten and Pliszka noted that therapeutic doses of stimulants improve prefrontal cortex function by increasing endogenous noradrenergic and dopaminergic stimulation of  $\alpha 2A$  and D1-receptors, respectively [35]. Furthermore, the NAR, an animal model of ADHD, has been reported to be inattentive, hyperactive, impulsive and depleted of serotonin in the prefrontal area [22, 36]. Under fatigue conditions, the increase of free tryptophan in the blood of NARs was higher than that in the control group. These findings provide evidence that metabolic imbalances between monoamines and tryptophan play an important role in the symptoms of ADHD.

These results suggest several possibilities for the relationship between monoamine function and ADHD symptoms: (i) ADHD symptoms are elicited by disturbance in the mutual regulation of the monoamine nervous system, (ii) monoamine imbalances arise in association with over-activation of serotonin release, (iii) potentiation of the kynurenine and serotonin pathways is relevant, [31, 32] and (iv) processes associated with metabolic activation of the kynurenine and serotonin pathways are key to understanding the mechanisms of central fatigue in ADHD (Fig. 2).

## Interactions and roles of glial cells and neurons in central fatigue

Tryptophan and its neuroactive metabolites in the brain play important roles in central fatigue. However, both glial cells (astrocyte or microglia) and neurons need to be taken together into consideration [18, 37], because there is an overwhelming number of glial cells in the brain [16]. Therefore, the role of glial-neuron interactions as a cause of attention deficit and central fatigue needs to be included. It is also necessary to clarify the fatigue-cognitive circuit as a link between the central and peripheral systems.

The author was the first to report that oligodendrocytes are involved in tryptophan metabolism [16]. Oligodendrocytes are involved in myelin sheath formation and development and are therefore associated with ADHD etiology.

In a rat model of central fatigue induced by chronic sleep disorder (CFSD), measurement of tryptophan levels at pre-synaptic terminals and in oligodendrocytes showed that presynaptic levels of tryptophan, kynurenine and kynurenic acid in the hypothalamus and hippocampus were higher in the CFSD group than in the control group. By contrast, serotonin levels were not elevated. Furthermore, the CFSD group had higher levels of tryptophan in oligodendrocytes. In this condition, the accuracy of spatial cognitive memory was impaired, and hyperactivity and impulsivity were also increased. These findings suggest that dynamic changes in oligodendrocyte-neuron interactions within the hypothalamic-hippocampal circuit cause central fatigue, and that increased tryptophan-kynurenic acid pathway activity in this circuit leads to cognitive decline. In addition, the plasma levels of tryptophan and kynurenine in the CFSD group were 1.5 times higher than in the control group. In rats receiving intraperitoneal kynurenine (100 mg/kg i.p.), kynurenine-treated rats showed enhanced production of kynurenic acid in the hippocampus and inhibited recall of retained spatial cognitive memories, as compared with the control group. The study revealed that the uptake of peripherally derived kynurenine and tryptophan into the brain enhances kynurenic acid production in the brain, and three factors (kynurenine, tryptophan and kynurenic acid) produce an amplifying effect that involves the role of central-peripheral linkage in central fatigue, leading to cognitive dysfunction. In summary, the explanatory path by which susceptibility to fatigue leads to attention deficit in ADHD can be associated with metabolic activation of the kynurenine and serotonin pathways.

## Conclusion and future directions

Understanding inattentive behavior in ADHD requires a focus on tryptophan levels. In a study that adopted this focus, levels of anthranilic acid, kynurenic acid and xanthurenic acid were found to be lower in adults with ADHD [8]. These results suggest that the tryptophan-kynurenine pathway hypothesis plays an important role in ADHD symptoms. However, since the assessment of ADHD is determined by behavioral characteristics in children up to the age of 12, future research will be needed to determine whether the results are similar to those for ADHD in adults. Previous studies have also reported that children with ADHD have increased levels of tryptophan and decreased levels of 3-hydroxykynurenine in blood [38]. This also

needs to be verified. Regarding the relationship between the tryptophan-kynurenine synergy hypothesis and ADHD, it is necessary to study the levels of tryptophan, kynurenine and tyrosine, a catecholamine precursor, in children with ADHD to determine the effect of concentration changes in the tryptophan-kynurenine pathway on the balance of monoamine activity in the brain.

In this regard, at the animal experiment level, it was pointed out that the NAR, which is a fatigue-prone rat, has a decrease in the monoamine system required for attention function in the prefrontal cortex and it has been proposed as an animal model for ADHD [22]. Moreover, there is a problem with monoamine balance [22, 31, 32]. We also pointed out that the inattention-type central fatigue score was significantly higher than the hyperactivity and impulsivity-type fatigue score [21]. More importantly, the relationship between attention and tryptophan metabolism should be investigated. Since there is a significant difference in plasma levels of tryptophan and kynurenine between adults with ADHD and healthy adults, and 78% of adults with ADHD exhibit intense symptoms of inattention [8], metabolic activation of the kynurenine pathway may induce the development of inattention in ADHD. To answer the question of whether these features, if observed in the tryptophan-kynurenine pathway, cause symptoms of inattention through their antagonistic effects on NMDA and  $\alpha 7$  nicotinic acetylcholine receptors, the correlation between alterations in the tryptophan-kynurenine pathway and performance of attention-based tasks in children with ADHD should be investigated.

We conducted a study using the AASS scale questionnaire in human adults. On the basis of assessment of 4 fatigue scale factors (mental fatigue, peripheral fatigue, sleep disorder and depression), participants were classified into 4 groups: inattention type, hyperactivity/impulsive type, mixed type groups, and a mixed type and non-mixed type control group. We reported that mental fatigue score was significantly higher in the mixed-type and inattention-type groups than the hyperactivity/impulsive type and control groups [21]. Furthermore, at the animal experiment level, it was pointed out that NAR, which is a fatigue-prone rat, has decreased activity in the monoamine system required for attention function in the prefrontal cortex [22]. These facts suggest a relationship between central malaise and attention-deficit ADHD.

Few studies have examined the relationship between tryptophan and the kynurenine pathway, which is a key to observing the dynamic metabolic kinetics of tryptophan. Since most of the tryptophan is metabolized along the kynurenine pathway, one future challenge will be to clarify the metabolic activity of the tryptophan-kynurenine pathway in relation to inattention and susceptibility to fatigue in ADHD.

Finally, BCAAs are already on the market as supplements and are widely used, and if the concentration is about 100 mg to 200 mg/kg used in our experiment (Fig. 1), even if the concentration of large neutral amino acids (LNAAs) other than that of tryptophan is decreased, side effects are unlikely at this dose level of BCAAs. On the other hand, today, the mainstream ADHD treatments methylphenidate, which suppresses the reuptake of dopamine and noradrenaline, and atomoxetine, which suppresses the reuptake of noradrenaline, eventually enhance the release of these neurotransmitters in the brain, resulting in the mitigation of ADHD symptoms. Guanfacine is also an agonist of the  $\alpha 2A$  receptor, which is a noradrenaline receptor present at the posterior synapse of pyramidal cells in the prefrontal cortex, and is said to enhance signal transduction and improve ADHD symptoms [39]. However, while these drugs have side effects, BCAAs have the advantage of being natural amino acids. However, the author's aim is to improve ADHD, which is associated with more inattention than hyperactivity and impulsive symptoms, and try to reduce inattention by removing easy fatigability as the main cause. Treatment with BCAAs is fundamentally different in concept from known treatments. Therefore, in reality, the combined use of conventional monoamine-based reuptake inhibitors and BCAAs can be considered. The synergistic effect and significance of these combinations are the subjects of future studies.

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