DOI: 10.26717/BJSTR.2018.04.001004

Masatoshi Yamashita. Biomed J Sci & Tech Res

ISSN: 2574-1241

Mini Review Open Access

Insight into Neurodevelopmental Disorders Related to the Imbalance of Monoamine Neuroactive Metabolites and Essential Amino Acids

Masatoshi Yamashita*[1], Masakazu Morinaga[2] and Takanobu Yamamoto[3]

[1]*Graduate School of Advanced Integrated Studies in Human Survivability, Kyoto University, Japan*

[2]*General Incorporated Association LITTO-LABO, Research Division of Psychology and Education, Japan*

[3]*Department of Psychology, Tezukayama University, Japan*

Received: April 17, 2018; **Published:** April 26, 2018

***Corresponding author:** Masatoshi Yamashita, Graduate school of Advanced Integrated Studies in Human Survivability, Kyoto University, 1 Yoshidanakaadachi-cho, Sakyo-ku, Kyoto 606-8306, Japan

Abbreviations: ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; HVA: Homovanillic Acid; 5-HIAA: 5-Hydroxyindoleacetic Acid; MHPG: 3-methoxy-4-hydroxyphenylglycol

Introduction

Attention deficit hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) are classified as neurodevelopmental disorders by DSM-5. ADHD is characterized by the behavioral symptoms including inattention, hyperactivity and impulsivity and also by moderate-to-severe academic and social impairment. In addition, ASD is characterized by impaired social interaction, impaired verbal communication, and repetitive behaviors. Brain monoamines and their neuroactive metabolites are thought to play key roles in neurodevelopmental pathology, but the specifics are still unknown. Here we provide the first evidence of a correlation between inattention, higher levels of 3-methoxy-4-hydroxyphenylglycol (MHPG), and lower levels of homovanillic acid (HVA); between hyperactivity/impulsivity, higher levels of HVA, and lower levels of MHPG; and between autistic symptoms, higher levels of MHPG, and lower levels of 5-hydroxyindoleacetic acid (5-HIAA). These correlations lend support to the hypothesis that monoamine imbalance is the basis of neurodevelopmental impairment. Moreover, recent findings show that inefficient monoamine synthesis induced by lack of essential amino acids, and mutation of the monoamine transporter genes in neurons at the junction between the peripheral and central nervous system, may contribute to the genesis of pathological behavior characteristic of neurodevelopmental disorders. This review aims to describe the main mechanism and further asks whether neurodevelopmental disorders are triggered by generation of essential amino acids, and these key enzymes.

Monoamine Imbalance Hypothesis

Studies on neurodevelopmental disorders have reported dynamic changes in three monoamine neurotransmitters (i.e., noradrenaline, dopamine, and serotonin) [1,2]. There is an accumulating body of evidence showing that administration of methylphenidate and atomoxetine lead to release and/or inhibition noradrenaline and dopamine uptake in the synaptic cleft and the effective reversal of neurodevelopmental disorders [3]. Moreover, serotonin 2A receptor antagonists (such as risperidone) and dopamine D2 receptor antagonists (such as haloperidol) reduce behavioral pathology in ASD [4]. It is interesting to note that neural-network control of noradrenaline, dopamine, and serotonin is involved in brain function impairment in neurodevelopmental disorders. In addition, to examine the effect of monoamine imbalance on neurodevelopmental disorders, we assessed the levels of urinary and salivary monoamine metabolites [5].

Approximately 60% of MHPG (a noradrenaline metabolite) excreted in the urine is from the central nervous system [6]. The dopamine metabolite HVA in urine [7] and the serotonin metabolite 5-HIAA in urine [8] are transported from the brain via different organic anion transporters located in the blood-brain barrier (BBB). Additionally, we showed that reduction of the serotonin level in the brain by 5,7-dihydroxytryptamine injection correlated with lower levels of 5-HIAA in urine [9]. Thus, it is notable that levels of neuroactive metabolites of monoamines in urine can be

used as biomarkers reflecting the activation of monoamine nervous system in the brain, and can be determined non-invasively by using urine and saliva. Some studies show reduced concentrations of urinary MHPG and HVA [10], and also decreased HVA concentration in cerebrospinal fluid (CSF), but not 5-HIAA [11] in ADHD patients relative to healthy controls. However, there are inconsistences; with one study showing that urinary HVA and 5-HIAA concentrations are lower in ADHD patients [12] and another showing that CSF HVA level is higher in ADHD patients [1].

Moreover, studies on ASD have found that CSF levels of MHPG, HVA and 5-HIAA involved with behavioral symptoms are increased in ASD [13]. However, Adamsen et al. [14] have pointed out that CSF levels of 5-HIAA were lower in ASD patients than in healthy controls [14]. On the basis of this evidence, there is a relationship between pathological behavior and monoamine imbalance in neurons at the interface between the peripheral and central nervous systems. The results of our analysis of neuroactive monoamine metabolite levels in urine and saliva indicated that these levels reflect indirectly the activation of the monoamine system in the brain [5,15]. Interestingly, correlations have been recently reported between inattention, higher levels of MHPG, and lower levels of HVA; between hyperactivity/impulsivity, higher levels of HVA, and lower levels of MHPG; and between autistic symptoms, higher levels of MHPG, and lower levels of 5-HIAA [5,15]. For example, serotonin neurons commonly receive sustained excitatory input from noradrenaline neurons, and furthermore regulate the mesolimbic and midbrain dopamine pathways [16]. This crosstalk between noradrenaline, dopamine, and serotonin is predicted to maintain the balance of monoamines in the brain. Here we provide the first evidence that links neurodevelopmental disorders to imbalances in monoamine levels.

The Relationship between Essential Amino Acids and Neurodevelopmental Disorders

Recently, studies showed that patients with neurodevelopmental disorders often had a history of fatigue, daytime tiredness [17,18], and daytime sleepiness [19]. Also, we have found that a high proportion of adults with chronic fatigue syndrome (CFS) experience comorbid anxiety and mood-related disorders [20]. Central fatigue, especially, also known as mental fatigue in humans, is implicated in CFS pathology [21], and leads to reduced mental task performance, disrupted social life, and impaired brain functions.

The strongest evidence supports the role of the tryptophan-serotonin pathway [22,23] and tryptophan-kynurenine pathway in central fatigue [24,25]. Tryptophan (C11H12N2O2) is an essential amino acid that binds to albumin in the circulation, and blood contains both free and bound tryptophan. Non-esterified fatty acids (NEFAs) also compete for the same binding site. Increases in the levels of NEFAs during central fatigue induced after exercise and postoperatively result in the dissociation of albumin and tryptophan [22,23].

This leads to increased passage of free tryptophan in the brain through the BBB and thus higher levels of serotonin in the brain through the enzymatic activity of tryptophan hydroxylase 2 (TPH2) [22,23]. Branched-chain amino acids (BCAAs) also compete with plasma free tryptophan for entry into the brain via system L transporter (LAT-1) located in the BBB [26]. If the concentration ratio of BCAAs decreases in the plasma, then the amount of free tryptophan to enter the brain increases. However, there is very interesting evidence that the 'tryptophan-kynurenine pathway' is involved in central fatigue [24,25]. In mammals, 95% of the tryptophan outside the serotonin pathway is metabolized via the kynurenine pathway [27]. Furthermore, we demonstrated that an enhancement of tryptophan-kynurenine-kynurenic acid pathway activity induces severe central fatigue, while decreasing the synthesis of serotonin and levels of BCAAs [24,25]. Like patients with ASD, patients with homozygous Branched Chain Ketoacid Dehydrogenase Kinase (BCKDK) mutations had lower levels of BCKDK messenger RNA and protein, E1α phosphorylation, and plasma BCAAs [28].

We have further found that Nagase analbuminemic rats had lower levels of serotonin in the prefrontal cortex, chronic enhancement of free tryptophan and lack of BCAA in the plasma, and higher levels of inattention, and hyperactivity/impulsivity [29]. In addition, autistic traits were present in patients carrying deleterious homozygous mutations in the gene encoding solute carrier transporter 7a5 (SLC7A5), which is a large neutral amino acid transporter located at the BBB [30,31]. A previous report has also found that mice lacking TPH2 are defective in brain serotonin synthesis and display behavioral symptoms of ASD, including impaired social interaction and communication and the propensity for repetitive behavior [32]. This may be the strongest evidence showing that imbalance between tryptophan and BCAA levels in the plasma and TPH2 gene and BCKDK gene mutations in the brain can induce inefficient synthesis of serotonin in the brain and cause the severe behavioral symptoms associated with neurodevelopmental disorders.

Conclusion

In summary, there is an accumulating body of evidence demonstrating that monoamines and their neuroactive metabolites are implicated in the behavioral symptoms associated with neurodevelopmental disorders. However, recent findings may indicate a connection between 'monoamine imbalance' and 'inefficient synthesis of serotonin' in neurodevelopmental disorders. Therefore, the relationship between essential amino acids involved with monoamine synthesis and key enzymes active in the genesis of neurodevelopmental disorders remains to be explored further.

References

1. Castellanos FX, Elia J Kruesi MJP, Marsh WL, Gulotta CS, Potter WZ, et al. (1996) Cerebrospinal fluid homovanillic acid predicts behavioral response to stimulants in 45 boys with attention-deficit hyperactivity disorder. Neuropsychopharmacology 14(2): 125-137.

2. Gorina AS, Kolesnichenko LS, Mikhnovich (2011) Catecholamines and their metabolites in children with Asperger and Kanner syndromes. Biomeditsinskaia khimiia 57(5): 562-570.

3. Hsia Y, Wong AY, Murphy DG, Simonoff E, Buitelaar JK, et al. (2014) Psychopharmacological prescriptions for people with autism spectrum

disorder (ASD): a multinational study. Psychopharmacology 231(6): 999-1009.

4. Stepanova E, Dowling S, Phelps M, Findling RL (2017) Pharmacotherapy of emotional and behavioral symptoms associated with autism spectrum disorder in children and adolescents. Dialogues in clinical neuroscience 19(4): 395-402.
5. Yamamoto T, Morinaga M, Yamashita M (2015) Balance hypothesis of behavioral characteristics and urinary monoamines metabolites in neurodevelopmental disorders. Journal of Neurochemistry (Suppl.1): 14.
6. Forssberg H, Fernell E, Waters S, Waters N, Tedroff J (2006) Altered pattern of brain dopamine synthesis in male adolescents with attention deficit hyperactivity disorder. Behavioral and Brain Functions 2: 40.
7. Mori S, Takanaga H, Ohtsuki S, Deguchi T, Kang YS, et al. (2003) Rat organic anion transporter 3 (rOAT3) is responsible for brain- to-blood efflux of homovanillic acid at the abluminal membrane of brain capillary endothelial cell. Journal of Cerebral Blood Flow & Metabolism 23(4): 432-440.
8. Ohtsuki S, Hori S, Terasaki T (2003) Molecular mechanisms of drug influx and efflux transport at the blood-brain barrier. Folia Pharmacological Japonica 122(1): 55-64.
9. Morinaga M, Shimizu T, Yamashita M, Yamamoto T (2017) The measurement of the quantity of urinary 5-hydroxyindoleacetic acid excretion as the noninvasive marker of the 5-HT content in the brain: About brain-urine correlation after the 5,7-dihydroxytryptamine microinjection. Japanese Journal of Cognitive Neuroscience 19(2): 95-101.
10. Walid OS, Javaid J, John MD, David BB (1983) Urinary MHPG and HVA excretion in boys with attention deficit disorder and hyperactivity treated with d-amphetamine. Biological Psychiatry 18(6): 707-714.
11. Shaywitz BA, Cohen DJ, Bowers MB (1977) CSF monoamine metabolites in children with minimal brain dysfunction: evidence for alteration of brain dopamine. A preliminary report. Journal of Pediatrics 90(1): 67-71.
12. Ryden E, Johansson C, Blennow K, Landen M (2009) Lower CSF HVA and 5-HIAA in bipolar disorder type 1 with a history of childhood ADHD. Journal of Neural Transmission 116(12): 1667-1674.
13. Gillberg C, Svennerholm L (1987) CSF monoamines in autistic syndromes and other pervasive developmental disorders of early childhood. British Journal of Psychiatry 151: 89-94.
14. Adamsen D, Meili D, Blau N, Thöny B, Ramaekers V (2011) Autism associated with low 5-hydroxyindoleacetic acid in CSF and the heterozygous SLC6A4 gene Gly56Ala plus 5-HTTLPR L/L promoter variants. Molecular Genetics and Metabolism 102(3): 368-373.
15. Morinaga M, Yamashita M, Yamamoto T (2016) The relationship between urinary monoamine metabolites dynamics balance and hyperactivity in the children with neurodevelopmental disorder: Comparison with the hyperactivity index of Strengths and Difficulties Questionnaire (SDQ). Tezukayama University Bulletin of Psychology 5: 41-47.
16. Stephen MS (2008) Stahl's essential psychopharmacology: neuroscientific basis and practical applications (3rd Edition). Cambridge University Press, UK.
17. Burhop J, Gibson J, de Boer J, Heydarian C (2018) Do You C What I C: Emergency Department Evaluation and Diagnosis of Pediatric Scurvy in an Autistic Child with a Restricted Diet. Pediatric Emergency Care.
18. Fisher BC, Garges DM, Yoon SY, Maguire K, Zipay D, et al. (2014) Sex differences and the interaction of age and sleep issues in neuropsychological testing performance across the lifespan in an ADD/ADHD sample from the years 1989 to 2009. Psychological Reports 114(2): 404-438.
19. Wiggs L, Sparrowhawk M, Barnett AL (2016) Parent Report and Actigraphically Defined Sleep in Children with and without Developmental Coordination Disorder; Links with Fatigue and Sleepiness. Frontiers in Pediatrics 4: 81
20. Afari N, Buchwald D (2003) Chronic fatigue syndrome: a review. American Journal of Psychiatry 160(2): 221-236.
21. Castell LM, Yamamoto T, Phoenix J, Newsholme EA (1999) The role of tryptophan in Fatigue in different conditions of stress. Advances in Experimental Medicine and Biology 467: 697-704.
22. Acworth I, Nicholass J, Morgan B, Newsholme EA (1986) Effect of sustained exercise on concentrations of plasma aromatic and branched-chain amino acids and brain amines. Biochemical and Biophysical Research Communications 137(1): 149-153.
23. Yamamoto T, Castell LM, Botella J, Powell H, Hall GM, Young A, Newsholme EA (1997) Changes in the albumin binding of tryptophan during postoperative recovery: a possible link with central fatigue? Brain Research Bulletin 43(1): 43-46.
24. Yamashita M, Yamamoto T (2017) Tryptophan circuit in fatigue: From blood to brain and cognition. Brain Research 1675: 116-126.
25. Yamamoto T, Azechi H, Board M (2012) Essential role of excessive tryptophan and its neurometabolites in fatigue. Canadian Journal of Neurological Sciences 39(1): 40-47.
26. Yamamoto T, Newsholme EA (2000) Diminished central fatigue by inhibition of the L-system transporter for the uptake of tryptophan. Brain Research Bulletin 52(1): 35-38.
27. Schwarcz R, Pellicciari R (2002) Manipulation of brain kynurenines: glial target, neuronal effect, and clinical opportunities. Journal of Pharmacology and Experimental Therapeutics 303(1): 1-10.
28. Novarino G, El Fishawy P, Kayserili H, Meguid NA, Scott EM, et al. (2012) Mutations in BCKD-kinase lead to a potentially treatable from of autism with epilepsy. Science 338(6105): 394-397.
29. Hakamada K, Yamamoto T (2014) The Nagase Analbuminemic Rats as an animal model of AD/HD. Japanese Journal of Cognitive Neuroscience 16(1): 67-76.
30. Tarlungeanu DC, Deliu E, Dotter CP, Kara M, Janiesch PC, et al. (2016) Impaired Amino Acid Transport at the Blood Brain Barrier Is a Cause of Autism Spectrum Disorder Cell 167(6): 1481-1494.
31. Maynard TM, Manzini MC (2017) Balancing Act: Maintaining Amino Acid Levels in the Autistic Brain. Neuron 93(3): 476-479.
32. Kane MJ, Angoa-Peréz M, Briggs DI, Sykes CE, Francescutti DM, et al. (2012) Mice genetically depleted of brain serotonin display social impairments, communication deficits and repetitive behaviors: possible relevance to autism. Plos One 7(11): e48975.

Submission Link: https://biomedres.us/submit-manuscript.php