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Neuropathology and Neuroendocrine Dysfunction in Autism Spectrum Disorder

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Neuropathology and Neuroendocrine Dysfunction in Autism Spectrum Disorder

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Abstract
Autism spectrum disorder (ASD) is a single spectrum disorder. It is characterized by marked social deficit, stereotype behavior, flexibility, sensory sensitivity, and language impairment. However, ASD can also be accompanied by neuropathology and neuroendocrine dysfunction. Higher testosterone level intrauterine is assumed to increase ASD risk in early childhood. There is limited research about the correlation between ASD and neuroendocrine dysfunction.

Keywords: Autism spectrum disorder; Neuroendocrine; Dysfunction.

1. INTRODUCTION

The prevalence of autism spectrum disorder (ASD) is about 1 in 59 8-year-old children in the United States [1]. ASD children are misdiagnosed with psychiatric disorders. Both disorders have same symptoms such as hyperactivity, anxiety, aggressive behavior, and depression. The differential diagnosis of ASD includes Rett's syndrome and selective mutism, communication disorder, intellectual disability, stereotypic movement disorder, ADHD, and schizophrenia. Some of the ASD patients cannot understand facial expression and emotion appropriately according to their age [2].

In ASD, there is different neuronal activation at amygdala, cerebrum, cerebellum, brain stem, and hippocampus related to several endocrine hormones. Neuropeptides, neurotransmitter, hormone, and hormone-like substance encode social behavior in developing brain [3].

2. NEUROPATHOLOGY

ASD involves multiple regression of brain, such as cerebrum, cerebellum, amygdala, and brain stem. Etiology is related to interaction between genetic and environmental factors. However, there is only limited research investigating neuroendocrine dysfunction in ASD [3].

2.1. Cerebral Cortex

Dorsolateral and medial parts of the frontal cortex grow larger than the rest of the cortex in the first year of life in ASD patients. Fusiform gyrus is important in face processing. There is significant reduction in neuron density layer and enhanced activation [4]. Temporal lobe is also affected in ASD [5].

2.2. Cerebellum

There are neuronal abnormalities in postmortem cerebellum of ASD patients. Decrease in mean Purkinje cell size, cerebellar gray, and white matter are some of the abnormalities. Those abnormalities will affect inhibitory neurotransmitter mechanism of action. The cerebellum projects the motor cortex, premotor cortex, frontal eye field, and frontal cortex. Selective genetic knock out of Purkinje cell causes ASD in mouse [6].

2.3. Amygdala

Decrease in neuronal size, increased neuronal packing density, and decreased complexity of dendritic arbors in hippocampus, amygdala, and other limbic structure were found in ASD. The amygdala is important in facial emotion recognition. There is precocious enlargement of amygdala that persists through late childhood. It starts at approximately 3 until 5 years old [4].

2.4. Spine
Increased density of the cervical spine is found in ASD patients. Abnormal spine generation and deficit in spine reorganization may contribute in amygdala and cortical overgrowth. Sometimes, it is followed by stunted growth in adolescence [4].

2.5. Hippocampus
Hippocampus is important in memory consolidation and retrieval. Larger hippocampus and increased cell packing density, but smaller neuron is found in ASD [4].

2.6. Nucleus Accumbens
Nucleus accumbens is related to social reward response in ASD. It is important in modulating the processing of reward and pleasure [5]. Modulation of the serotonin (5-HT) release in the nucleus accumbens bidirectionally modifies sociability in a mouse model. Serotonin release in nucleus accumbens rescues social deficits in mouse autism model [7].

3. NEUROENDOCRINE DYSFUNCTION

Several hormones are postulated to be related to ASD. Testosterone, cortisol, and oxytocin are the most common. Other hormones such as growth hormones, vasopressin (antidiuretic hormone), melatonin, thyroid hormone, and estrogen have some role in ASD risk [8].

3.1. Testosterone
Abnormal levels of testosterone in autistic children have been studied, and it may be the cause of violent behavior, explosive aggression, and nonexplosive aggression. In a study of 35 prepubertal ASD boys (3-10 years old), the testosterone level was determined by drawing venous blood. The results revealed that there was a positive correlation between testosterone level and hyperactivity [8].

Incidence of ASD is in line with extreme male brain (EMB) theory. This theory is based on the principle that the human brain has two important dimensions (i.e., empathizing and systemizing). In ASD, systemizing is overdeveloped and empathizing is underdeveloped. ASD boys were shown to have lower ratio second digit (index finger) to fourth digit (ring finger) than normal [9, 10]. It revealed higher levels of prenatal testosterone exposure that would increase ASD risk later in childhood life [9].

ASD women had a high androgenic state condition (higher testosterone level) such as polycystic ovary syndrome, an increased incidence of hirsutism (excessive growth of body or facial hair in women), irregular menstrual periods, delayed puberty, and bad acne. These women will have an increased risk of ASD children due to hyperandrogenic state [11]. Majewska *et al*. found that androgen levels were higher in prepubertal children with ASD, compared to the neurotypical patients. These conditions were more obvious in 7-9 years old ASD children. They revealed early puberty [11].

Davies (2014) studied that elevated androgen level prenatally might increase ASD risk. Higher testosterone level intrauterine may have a role in etiopathogenesis of ASD. Boys tend to have aggressive and externalized behavior rather than girls. He predicted that antiandrogen therapy might have potential value in ASD cases [12].

Pivovarciova *et al*. concluded that even though there was no significant association between testosterone level in plasma and hyperactivity symptoms, it was revealed that androgen receptor sensitivity might be related to hyperactivity symptoms. The effect of testosterone might be modulated through increased sensitivity of androgen receptor. Hyperactivity symptoms in ASD are enhanced by increased prenatal testosterone effects. This will increase androgen receptor sensitivity [9].

3.2. Cortisol
Cortisol is associated with increase in repetitive behaviors. Cortisol secretion is controlled by hypothalamo–pituitary–adrenal (HPA) axis. The role of cortisol is to help human to adapt toward environmental challenges (fight or flight mechanism). The secretion of this hormone increases in stress condition. This can lead to adrenal gland fatigue due to excessive secretion of cortisol [13]. Highest peak of cortisol release is 20-30 min after awakening. It is also known as cortisol awakening response (CAR). The CAR is influenced by genetic condition. It is important in orientation of self, time, and place. CAR dysfunction could be related to difficulties in adaptation with environmental changes. These conditions are frequent in individuals with ASD. ASD children had a decrease in morning cortisol and higher psychological measures of stress and sensory functioning. For this reason, an ASD patient should have a consistency in their daily routines and environment condition [9]. There are many other benefits to routine, but this can alleviate stress and stereotyped behaviors due to expectations being set and their insistence on sameness (IOS) [14].

3.3. Oxytocin
Oxytocin secretion is facilitated by estrogen. Oxytocin is associated with repetitive behavior, social recognition, and bonding. Amygdala activity can be attenuated by oxytocin. Through oxytocin mechanism of action, negative feelings and anxiety in ASD patients might be reduced. Patients would feel more secure in their social environment. Higher oxytocin level would overcome

negative feelings and compulsive behavior. Better daily living skills and social interaction are related to higher oxytocin level. The oxytocin receptor (OXTR) gene is located at the 3p25 region. There is a single nucleotide polymorphism of OXTR in children and adolescents with ASD [9].

Stereotyped behavior of children with ASD decreased significantly when they were given oxytocin infusion. They also had improvement in emotion recognition and repetitive behavior when they were given systemic oxytocin. However, larger cohort studies are needed to establish this result [9].

3.4. Insulin-like Growth Factor-1 (IGF-1)

Hyperinsulinemia in the prenatal period might lead to an alteration in brain development and regulation. This might increase the risk of developing ASD [15]. ASD patients tend to have larger brain with a rapid acceleration at 1-2 months old and 6-14 months old. IGF1, IGF2, insulin-like growth factor binding protein 3, and growth hormone binding protein levels are higher. However, further studies need to be done to explain it thoroughly [9].

There is controversy regarding IGF-1 levels in ASD patients. IGF-1 level in cerebrospinal fluid of ASD children was significantly lower than normal range. Lower IGF-1 level might cause cerebellar growth disruption. Purkinje cells in the cerebellum were not able to survive without normal concentration of IGF-1. Reduced number of Purkinje cells may cause reduced cerebellar activation. IGF-1 might be a promising treatment for ASD. However, longitudinal studies must be done to prove this hypothesis [16].

Urinary IGF-1 excretion was significantly lower in autistic children than in age-matched controls. In contrast, Marchetto *et al.* studied that there was higher levels of IGF-1 in children with ASD [17]. Insulin-like growth factor II targets the mTOR (mammalian target of rapamycin) pathway to reverse autism-like phenotypes in mice. Further trials will be needed to determine the exact efficacy of IGF-1 as a potential treatment in ASD patients [18].

3.5. Vasopressin

Arginine vasopressin is also known as antidiuretic hormone (ADH). The receptor distribution is throughout the nervous system, especially in cerebral cortex, the nasal septum, hypothalamus, and hippocampus. Two main types of vasopressin receptors are the V1a receptors (V1a R) and V1b receptors (V1b R). The V1aR gene has been related to ASD. V1aR and V1bR knock out (KO) mice had social interaction impairment. Vasopressin in humans (males) is associated with social signals and aggression. AVP facilitated agonistic responses in men and affiliative responses in women [20].

3.6. Melatonin

Melatonin is secreted by the pineal gland (or pineal body). It is important for photoperiod recognition, circadian and seasonal rhythm adjustment, sleep induction, and immune response facilitation. About 44-83% of ASD children had some levels of sleep disturbances. They are longer sleep latency, frequent awakenings, and decreased nonrapid eye movement (REM). This hormone is lower in ASD. It might be due to acetylserotonin *O*-methyltransferase (ASMT) deficiency in melatonin pathway. However, this condition is also connected to cortisol level [13]. Melatonin deficiency might cause abnormal synaptogenesis. Melatonin secretion is often impaired in ASD [19].

3.7. Thyroid Hormone

Thyroid hormones are important in neurogenesis such as cerebellum cell proliferation, synaptogenesis, and myelination. Lack of thyroid hormone in the neural development of fetal period might cause behavioral defect in ASD. However, extensive studies between thyroid hormone and ASD are not yet available [20].

3.8. Secretin

Secretin has primary function in digestion. It is also produced in cerebellum and hippocampus. The receptors are found in cerebellum, hippocampus, brainstem, cerebral cortex, thalamus, striatum, and amygdala. Secretin administration might improve language skills, cognition, memory, and behavior. Deficiency of secretin receptor in mice might cause rigid social phenotype and impaired social recognition, inability, which is similar to ASD condition [20].

4. CONCLUSION

ASD patients have neuropathology in cerebellum such as decrease in mean Purkinje cell size, cerebellar gray matter, and cerebellar white matter. Decrease in neuronal size, increase in neuronal packing density, and decrease in the complexity of dendritic arbors in hippocampus, amygdala, and other limbic structure were also found. Larger hippocampus and increased cell packing density, but smaller neuron is obvious in ASD patient. Neuroendocrine dysfunction in ASD is increase of testosterone level and decrease of some hormones, such as cortisol, oxytocin, IGF-1, melatonin, thyroid hormone, and secretin. Defect in arginine vasopressin receptor might also cause ASD. However, further cohort studies with larger population study are needed to establish the hypothesis.

References

1. Brook M. CDC: autism prevalence up slightly to 1 in 59. 2018. Available from: htpps://www.cdc.gov/media/releases/2018/p0426-autism-prevalence.html
2. Ferri SL, Abel T, Brodkin ES. Sex differences in autism spectrum disorder: a review. Curr Psychiatry Rep. 2018; 20(9):1-17.
3. Eisenberg IW, Wallace GL, Kenworthy L, Gotts SJ, Martin A. Insistence on sameness relates to increased covariance of gray matter structure in autism spectrum disorder. Mol Autism. 2015; 6(54):1-12. doi:10.1186/s13229-015-0047-7
4. Ha S, Sohn IJ, Kim NW, Sim HJ, Cheon KA. Characteristics of brains in autism spectrum disorder: structure, function and connectivity across the lifespan. Exp Neurobiol. 2015; 24(4):273-84.
5. Park HR, Lee JM, Moon HE, Lee DS, Kim BN, *et al*. A short review on the current understanding of autism spectrum disorders. Exp Neurobiol. 2016; 25(1):1-13.
6. Tsai PT, Hull C, Chu YE. Autistic like behavior and cerebellar dysfunction in Purkinje cell Tsl mutant mice. Nature. 2012; 488:647-51.
7. Walsh JJ, Christoffel D, Heifets BD, Ben-Dor GA, Selimbeyoglu A, *et al*. 5-HT release in nucleus accumbens rescues social deficits in mouse autism model. Nature. 2018; 560:589-94.
8. Pivovarciova A, Hnilicova S, Ostatnikova D, Mace FC. Testosterone and explosive aggression in autism spectrum disorders. Neuroendocrinol Lett. 2014; 35(7):553-9.
9. Pivovarciova A, Durdiakova J, Babinska K, Kubranska A, Vokalova L, *et al*. Testosterone and androgen receptor sensitivity in relation to hyperactivity symptoms in boys with autism disorders. PLoS ONE. 2016; 11(2):e0149657. doi:10.1371/journal.pone.0149657
10. Schieve LA, Tian L, Dowling N, Croen L, Fong JH, *et al*. Associations between the 2nd to 4th digit ratio and autism spectrum disorder in population-based samples of boys and girls: findings from the study to explore early development. J Autism Dev Disord. 2018; 48(7):2379-95. doi:10.1007/s10803-018-3495-z
11. Majewska MD, Hill M, Urbanowicz E, Rok-Bujko P, Bienkowski P, *et al*. Marked elevation of adrenal steroids, especially androgens, in saliva of prepubertal autistic children. Eur Child Adolesc Psychiatry. 2014; 23(6):485-98. Epub 2013/09/18. doi:10.1007/s00787-013-0472-0; PMID: 24043498; PubMed Central PMCID: PMC4042015
12. Davies W. Sex differences in attention deficit hyperactivity disorder: candidate genetic and endocrine mechanism. Front Neuroendocrinol. 2014; 35:331-46.
13. Yang CJ, Tan HP, Yang FY, Wang HP, Liu CL, *et al*. The cortisol, serotonin and oxytocin are associated with repetitive behavior in autism spectrum disorder. Res Autism Spectr Disord. 2015; 18:12-20.
14. Esler AN, Stronach ST, Jacob S. Insistence on sameness and broader autism phenotype in simplex families with autism spectrum disorder. Autism Res. 2018; 11(9):1253-63. doi:10.1002/aur.1975
15. Carpita B, Muti D, Dell'Osso L. Oxidative stress, maternal diabetes, and autism spectrum disorders. Oxid Med Cell Longev. 2018; 9:1-9.
16. Steinmetz AB, Stern SA, Kohtz AS, Descalzi G, Alberini CM. Insulin-like growth factor II targets the mTOR pathway to reverse autism-like phenotypes in mice. J Neurosci. 2018; 38(4):1015-29.
17. Marchetto MC, Belinson H, Tian Y, Freitas BC, Fu C, *et al*. Altered proliferation and networks in neural cells derived from idiopathic autistic individuals. Mol Psychiatry. 2016. doi:10.1038/mp.2016.95
18. Riikonen R. Insulin-Like growth factors in the pathogenesis of neurological diseases in children. Int J Mol Sci. 2017; 18:pii: E2056.
19. Jin YH, Choi JH, Won JY, Hong YG. The relationship between autism spectrum disorder and melatonin during fetal development. Molecules. 2018; 23(198):1-9.
20. Tareen RS, Kamboj MK. Role of endocrine factors in autistic spectrum disorders. Pediatr Clin North Am. 2012; 59:75-88. doi:10.1016/j.pcl.2011.10.013