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Review Article

The Role of Serotonin System Abnormality in the Risk of Autism Spectrum Disorders

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Abstract

Autism spectrum disorder (ASD) is a neurodevelopmental disorder with high heritability. The domain behavioral symptoms of ASD are impaired in social interaction, lack of communication, and are often accompanied by repetitive and stereotyped behaviours or interest. The spectrum of the disease applies to varying in cognitive functioning in those domain behaviors and thereby ASD term includes autistic disorder, Asperger's syndrome, pervasive developmental disorder not-otherwise specified. The worldwide prevalence of ASD is estimated to be about 1 in 161 children and it is one of the global mental health issues. However, there are no effective treatment or cure medications available and the challenges to finding a solution still remain. High serotonin level in the platelets or serotonin system abnormality and transient brain overgrowth are two most replicated findings in ASD research. The abnormality in serotonin system occurring in the brain as well as peripheral part of the body in ASD individuals, have been reported in several research findings. In this review, previous research reports on serotonin system abnormality in ASD are highlighted and discussed.

Keywords: *Autism Spectrum Disorders; Behavioral Abnormality; Serotonin; Serotonin System*

Background

Serotonin system has been overlooked in several researches concerning the abnormalities in mind and behaviors. And the deficits in serotonin system have been one of the major concerns in ASD research. ASD is not a fatal or infectious disease, but a highly complex genetic and neurodevelopmental disorder which causes lifelong disabilities in social interaction, social communication with restricted and repetitive behaviors and interests [1]; thus required a lifelong caregiver. And the symptoms of ASD appear when the child attains one and a half years of age [2,3]. The number of ASD continue to increase and the recent estimate in the United States reported by Centers for Disease Control and Prevention's (CDC) Morbidity and Mortality Weekly Report (MMWR) Surveillance Summary.is one in 59 among the children with 8 years of age [4,5]. Global prevalence from the earlier studies reported 62 in 10000 children which is equivalent to 1 in 161 individuals and consistently rate of ASD in males is always higher than the females in several studies [6].

Serotonin system and the behavior

Serotonergic system involves serotonin, serotonin receptors, serotonin transporters etc. The 5-hydroxy tryptophan (5-HT), commonly known as serotonin is a monoamine neurotransmitter produced in serotonin secreting neurons in the brain, enteric neural plexus, enterochromaffin cells of gastrointestinal mucosa, mast cells of various connective tissues and pinealocytes of pineal body of animals and humans. Both in the brain and peripheral part of the body serotonin is synthesized from the amino acid tryptophan in the similar synthetic pathways excepting the rate limiting enzymes. The rate limiting enzyme tryptophan hydroxylase 1 (TPH1) acts in the brain whereas its isoform tryptophan hydroxylase 2 (TPH2) acts in the peripheral system. Serotonin synthesis occurs mainly in the raphe nuclei of the brain and enterochromaffin cells of gastro intestinal tract. Since serotonin is strongly believed to control normal behavior, and thereby

any defect in this neurotransmitter system may lead to different behavioral alterations. Several studies have emphasized the roles in many psychiatric disorders that include stress, depression, drug addiction, obsessive compulsive disorders, attention-deficit hyperactivity disorder, schizophrenia, hallucinogenic drug action, autism, panic and anxiety disorders, aggression, and anorexia bulimia and the details are extensively discussed in different sections in the Book "Handbook of the Behavioral Neurobiology of Serotonin" [7]. Besides, role of serotonin has also been strongly implicated in wide range of processes such as cardiovascular and respiratory activity, sleep, aggression, sexual behavior, nutrient intake, anxiety, mood, motor output, neuroendocrine secretion, and nociception and analgesia behaviors [8].

Serotonin is one of the earliest formed neurotransmitter in mammalian brains [9,10]. In humans the development of serotoninergic neurons become evident by 5 weeks of gestation [11] and there is dramatic increase by the 10th week of gestation [12,13], where they are predominantly present in dorsal raphe nuclei [12]. In normally developing brains, serotonin synthesis continues to increase throughout gestation period until the first 2 years of life and the peak level at the age of 5 years is about the double of adult value [13]; after the age of 5 years the level declines to adult value [14]. Similar pattern is also observed for serotonin receptor $5HT_{1A}$ [15] and $5HT_{2A}$ [16] indicating role of these receptors during the early development period of life. Studies using rodent models also showed the similar pattern [17].

Dual nature of serotonin

The high level of serotonin observed during the early development stages reveals bifunctional characteristic of serotonin in the brain, acting as neurotrophic factor as well as neurotransmitter. Numbers of studies using animal models have exhibited self-regulatory action of serotonin during the earliest stage of life influencing development of its own neurons [17,18]. During the brain development process, serotonin functions in neurogenesis and neuroprotection [19], gliogenesis [20], migration [21], differentiation and maturation [22]. In adult brain, it is likely to be involved in the maintenance and plasticity as mentioned elsewhere [23]. It is interesting to note that synaptogenesis in human, which begins in midgestation [24] and peaks at about 2 years and begin to slow down during adolescence and adulthood [25]. This indicates role of serotonin in synaptogenesis of human and its time course is similar to the changes in serotonin level. In this process serotonin may act directly through $5\text{-}HT_{1A}$ receptor or indirectly through the release of tropic factor S100B [26]. Therefore, it is likely that any factor that causes the changes in the serotonin level during development may lead to changes in the brain morphology and function. There are also evidences that showed interferences in serotonin system development due to hypoxia [27], diet [28], infections [29], and environmental toxins like pesticides etc. [30]. These findings have brought concerns regarding the effects of maternal stress or drug during pregnancy for altering serotonin level [31]. In human, lower serotonin level in the infant was correlated with prenatal maternal cortisol level [32], while maternal depression during pregnancy also causes serotonin loss in the infant [33]. On the other hand, many studies using animal models for anxiety [34], autism [35], depression [36] and aggression [37] have shown that changes in serotonin level during development not only change the brain morphology but also the behavior. Furthermore, understanding the role of serotonin system in the brain had already made a large contribution in the etiology of many psychiatric disorders [7].

Serotonin system imbalance in ASD

Chugani., *et al*. (1999) have observed variation in the brain serotonin synthesis capacity between the autistic and non-autistic individuals using PET (positron emission tomography) scanning protocol [38]. Among the non-autistic children the capacity of synthesis was more than two times of the adult value until 5 years of age, and then continue to decline towards the adult value with the increase of age until 14 years; declination is earlier for girls compared to boys. On the contrary for autistic children, the serotonin synthesis capacity gradually increased between the age of 2 and 5 years at the rate of 1.5 times of the adult value [38]. The serotonin synthesis capacity alteration at this particular age period indicates disruption during the developmental process in autism. Meanwhile, serotonin synthesis capacity not reaching the developmental peak was also shown to be associated with altered language development [39,40]. Chugani., *et al*. in 1997 demonstrated variations in serotonin synthesis capacity at specific brain regions of autistic boys as it was found to decrease in the dentate-thalamocortical pathway while simultaneous increase was observed in the contralateral dentate deep cerebellar nucleus [40].

However, serotonin synthesis capacity becomes normal or may be more in adults with ASD [39,40]. Further, a more recent study using SPECT (single photon emission computed tomography) has demonstrated decrease in serotonin transporter binding capacity among individuals with ASD aged between 5 - 16 years. This was particularly evident in the medial frontal cortex area of the brain even though the lower binding capacity was also observed in the midbrain and temporal lobe areas [41]. Interestingly, the reduction was more apparent in adolescent individuals compared to younger ones [42] indicating participation of serotonin transporters during serotonin development. It was also pointed out that development of serotonin synthesis capacity in non-autistic children was positively correlated with the developmental variations in the cortical synaptic density during infancy and childhood [43]. The observations in 12 postmortem specimens indicated that the number of synapses was maximal at the age of 1 - 2 years and declined at the age 2 - 16 years [44]. Putting this idea Makkonen., *et al*. (2008) stated that it is possible to occur less synapse sprouting with a sparse density in serotoninergic pathways which will affect the serotonin transporter binding capacity for autistic individuals [42]. Subsequently, Chugani., *et al*. (2002 and 2005) have indicated that the interventions which enhance serotonergic neurotransmission during early childhood development can have the most immediate potential in elicitating clinically important adaptive brain changes in children with autism [45]. However, no clue is available for the link between the brain size and serotonin system.

High serotonin level present at the range of 30-50% in the platelets of ASD individuals has been consistently reported from different populations in several studies [46]. Studies using animals indicate high platelet serotonin level in ASD individuals which may be related to early decrease in central serotonin development. Exposing rats to serotonin agonist during mid-gestation to adolescent period leads to increased pre and postnatal serotonin level and that may result in the loss of central serotoninergic innervations in the pups, probably by autoregulation through $5HT_{1A}$ receptor [47]. Besides, $5\text{-}HT_{1A}$ knockout mice show high platelet serotonin level during development and adulthood while showing transient decrease in the brain during early and postnatal stage [48]. Studies with gestational tryptophan hydroxylase inhibition as well as tph1 deficient mice demonstrated that normal brain development and peripheral serotonin in offspring are direct consequence of peripheral and maternal serotonin availability during gestation [49]. These evidences indicate close link between central and peripheral serotonin level and its role in brain development even though the mechanism of regulation is yet to be understood. Since, abnormalities of serotonin function occur in ASD, understanding the mechanism of regulation of serotoninergic system will helpful in investigating the pathology of ASD. Interestingly, improvement of ASD behavioral symptoms after treatment with selective serotonin reuptake inhibitors has further supported the correlation between autistic behavior and serotonin system abnormality [50].

Conclusion

Serotonin plays dynamic roles during the neurodevelopmental processes. The abnormalities occurred in the serotonin system could affect brain and behavior leading to neurodevelopmental disorders such as ASD. There are several reports that indicate association of serotonin system in ASD. However, conclusive evidence is yet to be established. Further research digging to the causes of serotonin system abnormality in ASD could provide a clearer understanding on the pathophysiology of ASD that can provide a strategy for proper treatment and cure.

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Bibliography

1. Singh AS. “Genetic predominance of autism spectrum disorder and finding the risk genes”. *OA Autism* 2 (2014): 8.
2. Dahlgren SO and Gillberg C. “Symptoms in the first two years of life. A preliminary population study of infantile autism”. *European Archives of Psychiatry and Clinical Neuroscience* 238 (1989): 169-174.

3. Cox A., *et al.* "Autism spectrum disorders at 20 and 42 months of age: stability of clinical and ADI-R diagnosis". *Journal of Child Psychology and Psychiatry* 40 (1999): 719-732.

4. New studies estimate autism prevalence at 1 in 40. Organization for Autism Research (2019).

5. Autism prevalence rises in communities monitored by CDC (2020).

6. Elsabbagh M., *et al.* "Global prevalence of autism and other pervasive developmental disorders". *Autism Research* 5 (2012): 160-179.

7. Handbook of the Behavioral Neurobiology of Serotonin. Edited by Christian P. Müller and Barry L. Jacobs 21 (2010): 14.

8. Whitaker-Azmitia PM., *et al.* "Role of high affinity serotonin receptors in neuronal growth". *Annals of the New York Academy of Sciences* 600 (1990): 315-330.

9. Aitken AR and Tork I. "Early development of serotonin-containing neurons and pathways as seen in wholemount preparations of the fetal rat brain". *The Journal of Comparative Neurology* 274 (1988): 32-47.

10. Lauder JM. "Ontogeny of the serotonergic system in the rat: serotonin as a developmental signal". *Annals of the New York Academy of Sciences* 600 (1990): 297-313.

11. Sundstrom E., *et al.* "Neurochemical differentiation of human bulbospinal monoaminergic neurons during the first trimester". *Developmental Brain Research* 75 (1993): 1-12.

12. Shen WZ., *et al.* "Immunohistochemical studies on the development of 5-HT (serotonin) neurons in the nuclei of the reticular formations of human fetuses". *Journal of Pediatric Neurosciences* 15 (1989): 291-295.

13. Levallois C., *et al.* "Immunocytochemical demonstration of monoamine-containing cells in human fetal brain stem dissociated cultures". *Brain Research. Developmental Brain Research* 75 (1993): 141-145.

14. Chugani DC., *et al.* "Developmental changes in brain serotonin synthesis capacity in autistic and nonautistic children". *Annals of Neurology* 45 (1999): 287-295.

15. Toth G and Fekete M. "5-Hydroxyindole acetic excretion in newborns, infants and children". *Acta Paediatrica* Hungarica 27 (1986): 221-226.

16. Bar-Peled O., *et al.* "Fetal human brain exhibits a prenatal peak in the density of serotonin 5-HT1A receptors". *Neuroscience Letters* 127 (1991): 173-176.

17. Daval G., *et al.* "Transient expression of 5-HT1A receptor binding sites in some areas of the rat CNS during postnatal development". *International Journal of Developmental Neuroscience* 5 (1987): 171-180.

18. Basura GJ., *et al.* "Ontogeny of serotonin and serotonin2A receptors in rat auditory cortex". *Hearing Research* 244 (2008): 45-50.

19. Goldberg JI. "Serotonin regulation of neurite outgrowth in identified neurons from mature and embryonic Helisoma trivolvis". *Perspectives on Developmental Neurobiology* 5 (1998): 373-387.

20. Vitalis T., *et al.* "Embryonic depletion of serotonin affects cortical development". *European Journal of Neuroscience* 26 (2007): 331-344.

21. Lauder JM. "Roles for neurotransmitters in development: possible interaction with drugs during the fetal and neonatal periods". *Progress in Clinical and Biological Research* 163C (1985): 375-380.

22. Riccio O., *et al.* "Excess of serotonin affects embryonic interneuron migration through activation of the serotonin receptor 6". *Molecular Psychiatry* 14 (2009): 280-290.

23. Bielenberg GW and Burkhardt M. "5-hydroxytryptamine1A agonists. A new therapeutic principle for stroke treatment". *Stroke* 21 (1990): IV161-163.

24. Whitaker-Azmitia PM., *et al.* "Serotonin depletion in the adult rat causes loss of the dendritic marker MAP-2. A new animal model of schizophrenia?" *Neuropsychopharmacology* 12 (1995): 269-272.

25. Huttenlocher PR., *et al.* "Synaptic development in human cerebral cortex". *International Journal of Neurology and Neurotherapy* 16.17 (1982): 144-154.

26. Chugani HT., *et al.* "Positron emission tomography study of human brain functional development". *Annals of Neurology* 22 (1987): 487-497.

27. Azmitia EC. "Neuronal instability: implications for Rett's syndrome". *Brain and Development* 23.1 (2001): S1-S10.

28. Shiraishi M., *et al.* "Brainstem monoamine pathology of neonatal hypoxic-ischemic brain damage: a model of acute stage of neonatal asphyxia". *Brain Research* 1213 (2008): 120-126.

29. Serfaty CA., *et al.* "Nutritional tryptophan restriction and the role of serotonin in development and plasticity of central visual connections". *Neuroimmunomodulation* 15 (2008): 170-175.

30. Winter C., *et al.* "Dopamine and serotonin levels following prenatal viral infection in mouse--implications for psychiatric disorders such as schizophrenia and autism". *European Neuropsychopharmacology* 18 (2008): 712-716.

31. Aldridge JE., *et al.* "Alterations in central nervous system serotonergic and dopaminergic synaptic activity in adulthood after prenatal or neonatal chlorpyrifos exposure". *Environmental Health Perspectives* 113 (2005): 1027-1031.

32. Muneoka K., *et al.* "Prenatal dexamethasone exposure alters brain monoamine metabolism and adrenocortical response in rat offspring". *American Journal of Physiology* 273 (1997): R1669-1675.

33. Field T., *et al.* "Pregnancy anxiety and comorbid depression and anger: effects on the fetus and neonate". *Depression and Anxiety* 17 (2003): 140-151.

34. Field T., *et al.* "Prenatal depression effects on the fetus and the newborn". *Infant Behavior and Development* 27 (2004): 216-229.

35. Hohmann CF., *et al.* "Neonatal serotonin depletion alters behavioral responses to spatial change and novelty". *Brain Research* 1139 (2007): 163-177.

36. Lira A., *et al.* "Altered depression-related behaviors and functional changes in the dorsal raphe nucleus of serotonin transporter-deficient mice". *Biological Psychiatry* 54 (2003): 960-971.

37. Vataeva LA., *et al.* "Behavioral alteration in the adult rats prenatally exposed to para-chlorophenylalanine". *Brain Research* 1169 (2007): 9-16.

38. Chandana SR., *et al.* "Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism". *International Journal of Developmental Neuroscience* 23 (2005): 171-182.

39. Chugani DC., *et al.* "Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys". *Annals of Neurology* 42 (1997): 666-669.

40. Chandana SR., *et al.* "Significance of abnormalities in developmental trajectory and asymmetry of cortical serotonin synthesis in autism". *International Journal of Developmental Neuroscience* 23 (2005): 171-182.

41. Chugani DC., *et al.* "Altered serotonin synthesis in the dentatothalamocortical pathway in autistic boys". *Annals of Neurology* 42 (1997): 666-669.

42. Makkonen I., *et al.* "Serotonin and dopamine transporter binding in children with autism determined by SPECT". *Developmental Medicine and Child Neurology* 50 (2008): 593-597.

43. Bethea TC and Sikich L. "Early pharmacological treatment of autism: a rationale for developmental treatment". *Biological Psychiatry* 61 (2007): 521-537.

44. Huttenlocher PR. "Synaptic density in human frontal cortex - developmental changes and effects of aging". *Brain Research* 163 (1979): 195-205.

45. Chugani DC. "Role of altered brain serotonin mechanisms in autism". *Molecular Psychiatry* 7.2 (2002): S16-17.

46. Mulder EJ., *et al.* "Platelet serotonin levels in pervasive developmental disorders and mental retardation: diagnostic group differences, within-group distribution, and behavioral correlates". *Journal of the American Academy of Child and Adolescent Psychiatry* 43 (2004): 491-499.

47. Whitaker-Azmitia PM. "Behavioral and cellular consequences of increasing serotonergic activity during brain development: a role in autism?" *International Journal of Developmental Neuroscience* 23 (2005): 75-83.

48. Janusonis S., *et al.* "Ontogeny of brain and blood serotonin levels in 5-HT receptor knockout mice: potential relevance to the neurobiology of autism". *Journal of Neurochemistry* 99 (2006): 1019-1031.

49. Lauder JM., *et al.* "Maternal influences on tryptophan hydroxylase activity in embryonic rat brain". *Developmental Neuroscience* 4 (1981): 291-295.

50. Froehlich W. "Making a case to continue considering treatment with selective serotonin reuptake inhibitors for children with autism spectrum disorders". *Current Psychiatry Reports* 13 (2011): 170-173.

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