THE DEVELOPMENTAL DISRUPTIONS OF SEROTONIN SIGNALING MAY INVOLVED IN AUTISM DURING EARLY BRAIN DEVELOPMENT

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Abstract—Autism is a developmental disorder defined by the presence of a triad of communication, social and stereotyped behavioral characteristics with onset before 3 years of age. In spite of the fact that there are potential environmental factors for autistic behavior, the dysfunction of serotonin during early development of the brain could be playing a role in this prevalence rise. Serotonin can modulate a number of developmental events, including cell division, neuronal migration, cell differentiation and synaptogenesis. Hyperserotonemia during fetal development results in the loss of serotonin terminals through negative feedback. The increased serotonin causes a decrease of oxytocin in the paraventricular nucleus of the hypothalamus and an increase in calcitonin gene-related peptide (CGRP) in the central nucleus of the amygdale, which are associated with social interactions and vital in autism. However, hyposerotonemia may be also relevant to the development of sensory as well as motor and cognitive faculties. And the paucity of placenta-derived serotonin should have potential importance when the pathogenesis of autism is considered. This review briefly summarized the developmental disruptions of serotonin signaling involved in the pathogenesis of autism during early development of the brain.

Key words: autism, serotonin, hyperserotonemia, hyposerotonemia, calcitonin gene-related peptide, oxytocin.

INTRODUCTION

Autism is a neurodevelopmental disorder of unknown, probably heterogeneous etiology that manifests in toddler to preschool years (Bailey et al., 1996; Amaral, 2011). As described by Kanner in 1943, there are three core features in individuals with autism: (i) impairments in reciprocal social interactions, (ii) an abnormal development in the use of language, and (iii) restricted activities and interests (Association and DSM-IV, 1994). Core symptoms are behaviors that are frequently found in autism but are not exclusive to autism and may be shared across the spectrum of autism disorders (ASD). Associated symptoms can be grouped as follows: hyperactivity/inattention, aggression, tics, and sleep disorders (Gringras, 2000; Posey et al., 2004; Wiggs and Stores, 2004). It is estimated that 1 autism case could arise in 80–240 children born (Baron-Cohen et al., 2009, Baio, 2012). However, it has been noted that the incidence of autism showed significant increase in recent years (Hertz-Picciotto and Delwiche, 2009).

It is now well established that autism is a heritable complex genetic disorder (Rutter, 2000). While rare single mutations or chromosomal abnormalities are likely responsible for some cases, current models strongly suggest that inheritance of multiple interacting polymorphic loci contribute to a continuum of disease phenotypes in the majority of affected children (Veenstra-VanderWeele et al., 2004). However, epidemiological-based twin studies show that certain unknown environmental or stochastic factors instead of...
heritability may be important in either precipitating the disorder or influencing its severity (Scott and Deneris, 2005). In spite of the fact that there are various etiologies for autistic behavior, the possibility of a common neurochemical mechanistic feature, shared by multiple causes of autism, cannot be excluded (Chugani, 2002). For this purpose, the functional neuroimaging of groups of autistic subjects of unknown etiology is compared to nonautistic control groups in search of common biological substrates (Chugani et al., 1997, 1999; Cochran et al., 2013). What is more, neuropathological observations that have emerged over the past decade point toward early pre- and postnatal developmental abnormalities that involve multiple regions of the brain, including the cerebellum, cortical white matter, amygdala, brain stem, and cerebral cortex (Gadad et al., 2013).

Although the etiology of autism is not yet known, the relationship between autism and psychiatric disorders associated with abnormal serotonin (5-HT) activity and the relationship between autism and neurological comorbidities affected by serotonin dysregulation are intriguing. The attention given to these genes was initially stimulated by early findings of hyperserotonemia in approximately 30% of autistic individuals (Schain and Freedman, 1961). Tryptophan (the precursor of serotonin) depletion in autism can worsen repetitive behaviors (McDougle et al., 1996a). The positron emission tomography (PET) studies suggest altered serotonin synthesis rates in autistic children versus non-autistic siblings and epileptic children (Chugani et al., 1999). Furthermore, selective serotonin transporter inhibitors often reduce rituals and routines common to individuals with autism (McDougle et al., 1996b), and several variants of genes, which are important for serotonin system function, have been the subject of gene association studies in efforts to obtain genetic evidence in support of a link of certain alleles to autism susceptibility (Cook et al., 1997; Tordjman et al., 2001; Coon et al., 2005). Additionally, developmental disruptions of serotonin signaling in utero can lead to abnormal brain function at adult stages (Bonnin and Levitt, 2011). All these support the hypothesis that dysfunctional serotonin signaling contributes to abnormal autistic behaviors. In this review we summarized how serotonin affects brain development and involves in the pathogenesis of autism during early development of the brain.

OVERVIEW OF HUMAN SEROTONIN

In humans, as well as in most other mammalian species, serotonin is produced by two distinct enzymes, tryptophan hydroxylase (TPH) 1 and 2. The activities of TPH are most abundant in the brain raphe, gut, and pineal gland (where N-acetyltransferase converts serotonin to melatonin). Tryptophan hydroxylase 1 (TPH1), located in the pineal gland and gut enterochromaffin cells, is responsible for synthesizing most of the serotonin found in the body (Gershon, 2005). TPH2, restricted to neurons of the raphe nuclei and the enteric nervous system, is responsible for the synthesis of the remaining serotonin. Tryptophan is converted into 5-hydroxytryptophan (5-HTP) by TPH1, and then 5-HTP is further converted into serotonin by aromatic L-amino acid decarboxylase (AADC). Therefore, TPH is thought to be the rate-limiting enzyme in serotonin biosynthesis. Approximately 95% of the body’s serotonin is found in the bowel; more than 95% of that is produced by enterochromaffin cells and thus is synthesized by TPH1. Virtually all of the serotonin in the bloodstream is located in blood platelets, which take up overflow serotonin from the gut. It has been shown that the blood platelets contain no serotonin in knockout mice lacking the plasmalemmal serotonin transporter (SERT) (Chen et al., 2001). TPH gene and serotonin transporter (5HTT) gene (SLC64A) were the focus of many mood disorder studies (Risch et al., 2009; Karg et al., 2011).

Serotonin has a wide range of physiological functions. It is released by the enteric neurons and enterochromaffin cells and regulates a variety of physiological functions in the periphery, such as intestinal motility, platelet aggregation, and vasconstriction (Gershon et al., 1977). Serotonin captured by platelets have a role in injury where serotonin release can alter blood flow (Vanhoutte and Lüscher, 1986) as well as stimulating the production of adhesive alpha-granular proteins in activated platelets (Walther et al., 2003). As indicated previously, abnormal levels of platelet serotonin have been observed in ASD-diagnosed children and their relatives (Ritvo et al., 1970; Abramson et al., 1989; Piven et al., 1991; Goldberg et al., 2009).

In the central nervous system (CNS), serotonin plays a role as neurotransmitter/neuromodulator, and also functions as a developmental signal (Celada et al., 2013). Serotonergic neuronal networks are among the earliest developing neurotransmitter systems in the mammalian brain and eventually grow into the most widely distributed biogenic amine networks (Lauder, 1990). After its release from serotonergic neurons, serotonin will bind its receptors at the synaptic site to activate intracellular signaling pathways to induce physiological effects. Based up on their pharmacological profiles, cDNA-deduced primary sequences and signal transduction mechanisms, 5-HT receptors are classified into seven subfamilies, 5-HT1 to 5-HT7, which comprise 14 receptor subtypes (5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F, 5-HT2A, 5-HT2B, 5-HT2C, 5-HT3, 5-HT4, 5-HT5A, 5-HT5B, 5-HT6, and 5-HT7) associated with unique genes. With the exception of the 5-HT3 receptor, a pentameric ligand-gated ion channel composed of several subunits (up to five different ones have been identified), the rest of 5-HT receptors belong to the super family of G-protein-coupled receptors and their activation results mainly in modulatory actions in the neurons expressing these receptors (Hoyer et al., 1994). The behavioral effects of serotonin are numerous as it regulates mood, appetite, body temperature, arousal, pain sensitivity, sexual behavior and hormone release (Lam et al., 2006). The actions of serotonin are
then terminated when it is rapidly taken up by a serotonin reuptake transporter (SERT).

In the brain, serotonergic neurons are generated early in development, during the first month of gestation in primates (Levitt and Rakic, 1982). One day after their generation, raphe neurons can synthesize serotonin and begin to extend profuse axon tracts: the caudal group projects into the spinal cord and the rostral group into the forebrain. The full maturation of the axon terminal network requires more time and is achieved only after birth in rodents (Lidov and Molliver, 1982). The neurons that produce serotonin are located in a restricted zone of the brainstem. Most are found in the raphe nuclei, on the midline of the rhombencephalon, with a smaller number in the reticular formation, but project their axons into various cortical and subcortical regions and innervate target tissues (Benes et al., 2000). Brainstem serotonin neurons send ascending projections that terminate in a defined and organized manner in cortical, limbic, midbrain, and hindbrain regions (Berger et al., 2009). All brain regions express multiple serotonin receptors in a receptor subtype-specific fashion. CNS serotonin neurons are thus positioned to modulate the activity of a wide variety of human brain circuits, which explains, in part, the pleiotropic behavioral effects of brain serotonin (Roth, 2006).

**SEROTONIN AND AUTISM**

Serotonin has specific functions in the CNS and in the periphery where it regulates many physiological activities. In rodent studies, decreased or increased brain serotonin during the postnatal period of development results in the disruption of synaptic connectivity in sensory cortices in the brain (Mitchell et al., 1990; Meaney et al., 1994; Gaspar et al., 2003). In human studies, serotonin has been demonstrated to be important for prenatal and postnatal brain development (Whitaker-Azmitia, 2001). Problems in serotonergic signaling in some of these systems have been implicated as comorbidities that occur with autism (Meyer, 2013). There has been a longstanding interest in serotonin's role in autism since 1961, when the abnormalities of serotonergic function in autism were first recognized by Schain and Freedman (Schain and Freedman, 1961). In past years, the "hyperserotonin hypothesis" in the developing brain has been commonly accepted. However, more and more studies supported that hyposerotonin may also be a cause of autism.

**Hyperserotonin and autism**

Excess serotonin during embryonic and early development has been shown to cause autism-like behaviors in rodents, and this theory often linked the conflicting high blood but low brain serotonin levels observed in both autistic children and developmental hyperserotonemia (DHS) model (McNamara et al., 2008). The mice that conversion of a single amino acid, Gly56, in serotonin transporter (SERT) exhibit significantly increased serotonin in whole blood, and display alterations in social function, communication, and repetitive behavior (Veenstra-VanderWeele et al., 2012).

High serotonin levels in blood. Most peripheral serotonin is found in the enterochromaffin cells of the intestine and in the platelet. Determination of urinary concentrations of the serotonin metabolite 5-hydroxyindole-acetic acid (5-HIAA) is useful in carcinoid diagnosis (Brand and Anderson, 2011). Recent reports on new and important roles of serotonin in the periphery have served to increase interests in circulating serotonin. Relevant findings include the possible requirement for maternally derived serotonin in mammalian embryogenesis (Côté et al., 2007), the role of gut-derived serotonin in bone growth regulation (Anderson et al., 2009), the roles of peripheral serotonin in liver regeneration and mammary gland development (Lesur et al., 2006; Dempsie et al., 2008; Laporta et al., 2013), and the importance of pancreatic extracellular serotonin in the control of insulin secretion (Isaac et al., 2013). Nearly all circulating serotonin is found sequestered within the dense granules of the platelet and is physiologically active only after platelet activation, degranulation, and release into the plasma. This platelet storage pool has been assessed by measuring serotonin in the whole blood or in platelet-rich plasma (PRP).

A potential role of the serotonergic system in autism has been suggested by the finding of hyperserotonemia (the increase of serotonin in blood) in a proportion of autistic subjects and a well-replicated change since the research by Schain and Freedman in 1961 (Hanley et al., 1977; Cook et al., 1993, 1994; Kahne et al., 2002; McNamara et al., 2008). This result has been extended with the recognition that blood serotonin is also elevated in their first-degree relatives (Abramson et al., 1989; Leboyer et al., 1999; Piven and Palmer, 1999). Paralleling blood serotonin studies in autistic patients, in utero exposure to drugs that raise blood serotonin levels, including cocaine and alcohol, increase rates of autism in children (Davis et al., 1992; Nanson, 1992). Both pregnant woman and fetus contributes to serotonin during pregnancy. Maternal circulation source of serotonin may be provided to the embryo before and during placentation, and may affect very early events of embryonic development, especially of brain's development (Côté et al., 2007). Similar synthetic capability was observed in the early human placenta, there is a placental serotonin influence on brain development during human pregnancy. And there is a progressive switch from an early dependence on an exogenous (placental) source of serotonin to a later endogenous brain source (Bonnin and Levitt, 2011). The well-replicated platelet hyperserotonemia of autism remains unexplained. Possible explanations for the increased exposure of the platelet to serotonin may due to the alteration in the platelet's handling of serotonin (Anderson et al., 2012). Studies on assessing platelet serotonin exposure have measured urinary 5-HIAA or serotonin excretion and platelet-poor plasma (PPP) serotonin levels (Connors et al., 2006; Mulder et al., 2012).
And the measurement of the much smaller but potentially critically important pool of human free plasma serotonin in PPP appears to provide the most direct and best available index in vivo exposure of the platelet to serotonin. However, the range of reported concentrations was big, from 0.6 to 179 nmol/L (Brand and Anderson, 2011), and some studies reported lower mean levels of PPP serotonin in autism compared to controls (Vered et al., 2003; Spivak et al., 2004; Connors et al., 2006), while the others reported no difference when compared to family member controls (Anderson et al., 2012). Therefore, the further researches of measuring free plasma serotonin in PPP are needed.

Low brain serotonin levels. As serotonin can not cross the blood–brain barrier, it is synthesized and regulated independently in each compartment. However, during perinatal development, the blood–brain barrier is not formed completely and serotonin can cross from the peripheral compartment into the brain freely (Blazevic et al., 2012). The recent studies showed that maternal serotonin levels may be especially important for early brain development, because radiolabeled \([^{11}C]\) serotonin injected into pregnant rats crosses the placenta and can be detected in the fetal brain, albeit in small amounts (Koren et al., 1966). Therefore, peripheral serotonin levels seem to have a role during pregnancy through maternal (Côté et al., 2007) and placental (Bonnin et al., 2011). At early stages of development, this serotonin can enter the brain of a developing fetus, and plays a negative feedback role on its own neurons by inhibiting cyclic AMP (cAMP) synthesis, and causes loss of serotonin terminals. In addition, high levels of serotonin during early brain development, as in autistic children or rats exposed to a serotonin agonist, result in a loss of serotonin terminals in the adult brain (Whitaker-Azmitia and Azmitia, 1986; Depolarization, 1995). Rick et al. revealed that the density of the serotonin transporter (SERT) immunoreactive fibers decreased about 40% in the olfactory bulb (OB) of citalopram (selective 5-HT reuptake inhibitor) exposed male rats, and this new findings may offer insight into the abnormal olfactory perception often noted in patients with ASD (Zhang et al., 2013). PET studies have revealed decreased radiolabeled activity of alpha-[\(^{11}C\)]methyl-L-tryptophan (a tracer for serotonin) in the frontal cortex and thalamus as well as lowered serotonin synthesis in autistic boys aged 2–5 (Chugani et al., 1999; Asano et al., 2001). Other reports from living subjects indicate that the serotonin system may be reduced in autism (Zafeiriou et al., 2009). For instance, methyl tryptophan retention was reduced in the left frontal cortex and thalamus in five of seven boys and in the right frontal cortex and thalamus in the two remaining autistic boys. A recent study discovered subjects with the Asperger’s syndrome showed a significant reduction in cortical 5-HT\(_2\)A receptor binding in the total, anterior, and posterior cingulated; bilaterally in the frontal and superior temporal lobes; and in the left parietal lobe. The study suggested that the reduced receptor binding was significantly related to abnormal social communication (Murphy et al., 2006). The loss of serotonin innervation persists throughout subsequent development and the appearance of autistic symptoms (Whitaker-Azmitia, 2005). Furthermore, the theory was further confirmed in animal studies. 5-Methoxytryptamine (5-MT) has the ability to cross the blood–brain barrier and is commonly used in studies testing the effects of excess serotonin on multiple disease models including autism (Whitaker-Azmitia, 2005). Besides in regulating the development of the neurons which produce it, serotonin may also play a role in neurochemical imprinting – that is, changes in behavior in the adult may be due to changes in neurochemistry during development, even though that neurochemistry may have been corrected by the time the animal becomes an adult (Shemer et al., 1991). Therefore, Whitaker-Azmitia assumed that high levels of serotonin in the blood seen in some autistic children (the so-called hyperserotonemia of autism) occur throughout development. This theory may explain the conflicting high blood – but low brain – serotonin levels observed in subjects with autism.

Oxytocin (OT) and calcitonin gene-related peptide (CGRP) may be involved in serotonin-induced autism. Serotonin terminals innervate both the paraventricular nucleus of the hypothalamus (PVN) and the central nucleus of the amygdala from cell bodies that originate in the dorsal raphe nucleus. The release of CGRP and OT is mediated by 5-HT1A and 5-HT2 receptors (Petrov et al., 1994; Jørgensen et al., 2003). Treatment with 5-MT causes a loss of OT immunoreactivity in the PVN and an increase of CGRP in the central nucleus of the amygdale. These two brain areas are known as heavy innervation from serotonergic dorsal raphe neurons, and cellular responses to serotonin had been suggested to play roles in autism (Whitaker-Azmitia, 2005). In addition, serotonin plays a direct and acute regulatory role in activity-dependent hippocampal neurogenesis (Klempin et al., 2013), which is involved in social behavior, and humans with autism usually exhibit a number of abnormalities in the hippocampus (Mercier et al., 2012). Increased hippocampal neurogenesis is related to the long-term maintenance of social avoidance. When neurogenesis was ablated by X-ray irradiation, significantly fewer mice displayed social avoidance. Thus, hippocampal neurogenesis appears to be involved in the persistent social avoidance behavior (Lagace et al., 2010).

OT is a nine-amino-acid peptide (nonapeptide) that is synthesized in the magnocellular neurosecretory cells in the brain’s hypothalamic PVN and supraoptic nuclei. It is released into the blood from the posterior lobe of the hypophysis, as well as directly from the perikarya, dendrites or axon collaterals of magnocellular neurons in response to sexual stimulation, uterine dilation, nursing, and stress in some situations. OT fibers have endings in a variety of different brain areas, including thalamus, hippocampus, amygdala, pineal gland and cerebellum (Insel and Young, 2000). In addition to
facilitate uterine contractions during parturition and milk letdown, OT and the structurally similar peptide, vasopressin (two amino acids differentiate them), have also been found to be critically involved in affiliative behaviors, including sexual behavior, mother–infant and adult–adult pair-bond formation, separation distress, and other aspects of social attachment. Finally, OT has been found to be involved in regulating feeding, grooming, and stress response (Hollander et al., 2007). Given that deficits in social interaction and affiliation are a core feature of autism and that OT is involved in the regulation of affiliative behaviors, it is believed that OT might play a role in autism (Waterhouse et al., 1996; Teng et al., 2013). The nucleus accumbens receives OT-receptor-containing inputs from several brain regions, and genetic deletion of these receptors specifically from the dorsal raphe nucleus, which provides serotonergic innervation to the nucleus accumbens, abolishes the reinforcing properties of social interaction. Furthermore, OT-induced synaptic plasticity requires activation of nucleus accumbens 5-HT2B receptors, the blockade of which prevents social reward (Dolen et al., 2013). Autistic children as a group showed lower OT levels than normal children (Modahl et al., 1998). OT administration facilitated the processing and retention of social information in adults diagnosed with autism or Asperger’s disorder: compared with subjects who received placebo first, subjects who received OT first showed increased retention of affective speech comprehension after a delay (Hollander et al., 2007). These findings are similar to previous reports in which OT administration reduced repetitive behaviors in adults with autism or autism spectrum disorders (Hollander et al., 2003). What’s more, the findings reveal that OT nasal spray improves emotion recognition for young people with autism spectrum disorders (Guastella et al., 2010). A role for OT in genetic risk for ASD is supported by many researches (Meyer-Lindenberg et al., 2011), two single nucleotide polymorphisms (SNPs) in the third intron of the OT receptor (OXTR) have emerged as particularly promising candidates in the recent ASD literature: rs53576 (G to A) and rs2254298 (G to A). In several studies, these polymorphisms were over transmitted in families to offspring with ASD, and formed a central component in ASD-related haplotypes (Wu et al., 2005). Further evidence for the important role of the OT system in autism comes from the work on CD38, a transmembrane protein that is involved in OT secretion in the brain and strongly influences social behavior. Interestingly, several genetic variants on the CD38 gene were identified that show a significant association with high functioning autism (Munesue et al., 2010).

The amygdala is considered to hold a significant role in autism, mainly through its involvement in the developmental deficit in emotion processing and, generally, in social perception (Schultz, 2005). Recent work shows that amygdala response to social stimuli in ASD, which may contribute to social symptoms, is genetically influenced (Wiggins et al., 2013). Also the volume change of the right amygdala was correlated with the capability to establish appropriate eye contact (Barnea-Goraly et al., 2014), which is an impaired ability in autism that is related to amygdala function (Adams et al., 2012), indicating the important role of serotonin in mediating and coordinating functions in these regions. A recent study, employing a different MR image analysis approach to that described in the present report, found increased gray matter density in the amygdaloid and periamygdaloid cortices of people with autism (Abell et al., 1999).

CGRP is a neuropeptide neuromodulator known to be highly localized to various sensory pathways, including the central nucleus of the amygdala, in a similar manner in rat and human (De Lacaile and Saper, 2000). Several lines of evidence indicate that the CGRP-immunoreactive fiber plexus in the central nucleus arises from neurons in the parabrachial nucleus. Within the amygdala, CGRP terminals are visible as a dense innervation of cell bodies, many of which are corticotrophin release factor (CRF) neurons. The immunohistochemical data demonstrate CGRP-containing neurons within subnuclei of the parabrachial nucleus that are known to project to the central amygdaloid nucleus (Schwaber et al., 1988), and CGRP projections to the amygdala are involved in conditioned response to acoustic and somatosensory stimuli and play a role in fear conditioning in social interaction (Kocorowski and Helmstetter, 2001).

**Hyposerotonemia and autism**

Recently, a report showed an increase in serotonin axons in postmortem brain tissue form autism donors relative to controls both in children and adults (Azmitia et al., 2011). Those findings are difficult to be explained by the “hyperserotonemia hypothesis”, because the theory predicts that hyperserotonin situations in the developing forebrain cause a compensatory decrease of serotonin axons as discussed above (Hadjikhani, 2010). However, the increase of serotonin axons may be explained if there are transient hyposerotonemia situations in the developing forebrain. In addition, Connors have reported that plasma serotonin levels in autism mothers were significantly lower than in mothers of typically developing children (Connors et al., 2006), indicating a possibility that maternal serotonin transplacentally transported into the fetus forebrain is not enough. Treatment of pregnant rats with a serotonin depletor during gestation results in offspring that exhibit behavioral and anatomic abnormalities analogous to those present in autism, such as passive avoidance, lack of inhibition (Shemer et al., 1988), decreased pain sensitivity, altered cortical and hippocampal brain morphology (Butkevich et al., 2003), and abnormalities in 5-HT receptor numbers in the brain (Whitaker-Azmitia et al., 1987). Recently, a research found reduced levels of some genes involved in the synthesis of serotonin in the lymphoblastoid cells from patients with ASD (Bocculo et al., 2013). Thus, a hypothesis that hyposerotonemia situations in the developing forebrain may cause autism must be considered.
Decreased concentrations of serotonin may affect the early brain development by exerting its neurotrophic actions through serotonin receptors and is involved in various events including control of proliferation, migration, cell death, synaptogenesis and establishing neuronal network (Gaspar et al., 2003). Mice that received neonatal injections of the serotonergic neurotoxin, 5,7-dihydroxytryptamine (5,7-DHT) into the major afferent pathway to the medial forebrain bundle (mfb), showed significantly increased cortical width, which is similar to the increased cortical volume described in children with autism. These results suggested that forebrain neonatal serotonin depletion may cause permanent morphologic changes in the structure of the cerebral cortex (Boylan et al., 2007). The rats injected with DL-P-chlorophenylalanine (PCPA, a reversible inhibitor of 5-HT synthesis) during the E12–17 stage of embryonic development, when major events in corticogenesis take place, showed altered maturation of pyramidal neurons of layers III and V of the somatosensory cortex, with these cells displaying reduced dendritic arborization and complexity (Vitalis et al., 2007). Postmortem microscopic evaluation of the brain tissue from adults with autism demonstrates abnormalities in cerebral cortical development, including increased cortical thickness and neuronal density, neuronal disorganization related to abnormal migration, poorly differentiated gray-white matter boundaries and an increased number of white matter neurons (Bailey et al., 1998). Thus, structural pathologies in autism cortex are consistent with observations from animal studies of altered cortical serotonergic innervation, suggesting that altered serotonin tone and altered brain development in autism may be causally related.

It has been shown that tryptophan depletion impairs learning and memory (Schmitt et al., 2000), the process of topographical matching of afferent and target neurons and the underlying wiring principles seem to be relevant to the development of sensory as well as motor and cognitive faculties (Inan and Crair, 2007), in addition, isocaloric, normoproteic, low tryptophan diet alters the fine tuning of topography in the visual system. The data also suggests a developmental delay in axonal elimination, a crucial step for neural circuitry organization or misplaced connections in retinotectal projections (González et al., 2008). Cote et al. have shown that, using TPH-1 knockout mice, (i) maternal serotonin is involved in the control of morphogenesis during developmental stages that precede the appearance of serotonergic neurons and (ii) serotonin is critical for normal murine development. Therefore, lower concentrations of serotonin in this period might also cause disturbance of the neuronal network, which is repeatedly reported as major abnormalities in autism brain.

In all, decreased neonatal serotonin can alter cortical morphogenesis in ways that are consistent with the neuropathology in autism. And the role of hyposerotonemia in autism deserves to be further studied and valued.

**SUMMARY**

In this review, we briefly summarized the neurobiological role of serotonin in the causes of autism. Pharmacological studies initially showed that serotonin can modulate a number of developmental events, including cell division, neuronal migration, cell differentiation and...
synaptogenesis (Gaspar et al., 2003). Additionally, a number of serotonin receptors show early and dynamic expression during development, and the overactivation or invalidation of certain serotonin receptor subtypes causes permanent alterations in the maturation of selected brain circuits. So, both the excess or decrease of serotonin raises the possibility that early changes in serotonin homeostasis are involved in the physiopathology of psychiatric diseases, such as anxiety disorders, drug addiction and especially autism (Whitaker-Azmitia, 2001; Gross et al., 2002), the possible mechanisms were illustrated in Fig. 1. The causes of homeostasis of serotonin need to be further investigated.

However, the direct evidences for hyposerotonemia in autism are relatively inadequate compared with hyperserotonemia, further researches on the influence of hyposerotonemia on early brain development need to be further investigated. Firstly, in human studies, a prospective multi center study about the relation between the blood serotonin level of mothers and the incidence of the autism are urgently needed. Secondly, studies on animal models of selective neonatal serotonin depletion or knockout are also important, including the development of serotonergic systems, cortical morphogenesis and autism-related behaviors. Further, it is possible that a closer analysis of the fine cortical morphogenesis and autism-related behaviors. Including the development of serotonergic systems, cortical morphogenesis and autism-related behaviors. This improved understanding may ultimately lead to new strategies for the prevention or cure of autism.

COMPETING INTERESTS

The authors declare that they have no competing interests.

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