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REVIEW

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 stereo typical 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.

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Abbreviations: ASD, autism disorders; CGRP, calcitonin gene-related peptide; CNS, central nervous system; 5-HT, serotonin; 5-HTP, 5-hydroxytryptophan; 5-HIAA, 5-hydroxyindole-acetic acid; 5-MT, 5-methoxytryptamine; OT, oxytocin; PET, positron emission tomography; PPP, platelet-poor plasma; PVN, paraventricular nucleus of the hypothalamus; TPH, tryptophan hydroxylase; TPH1, tryptophan hydroxylase 1.

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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 vasoconstriction (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