5

Serotonergic Neurotransmission in Autism Spectrum Disorders

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1. Introduction

Serotonin (5-hydroxytryptamine, 5-HT) was isolated and characterized during the late 1930s through the 1950s. Since then, serotonin has been shown to play a key role in a range of behaviors and processes, including sensory gating and processing, behavioral inhibition, appetite, aggression, sleep, mood, and neuroendocrine secretion (Anderson, 2005). The serotonin neuron system stretches abundant branches from a limited number of cells in the brain stem and widely and densely projects the brain (Takeuchi, 1988). Therefore, the serotonin neuron system is considered to be "the total control system". During development of the brain, the serotonin neuron system is not only essential for formation and maintenance of synapses (Lauder, 1990), but also is affected by a variety of environmental factors. These findings are crucial for understanding the pathogenesis of many developmental disorders. This paper reviews the involvement of the serotonin neuron system in neurotransmission in autism spectrum disorders.

2. Anatomical characteristics of the serotonin neuron system

The distribution of the serotonin neuron system overwhelms that of other neuron systems (Nieuwenhuys, 1985; Takeuchi, 1988). The serotonin neuron system is a slow synaptic potential system with a long time lapse, similar to the physiology of noradrenalin and dopamine neuron systems. In this review, we examine the central nervous system (CNS) in monkeys (macaca fuscata) describing the anatomical characteristics of the serotonin neuron system, in order to understand the diversity of functions of serotonin in the brain and the pathogenesis of developmental disorders.

2.1 Cell bodies of serotonin neurons are localized in the brain stem

The cell bodies of serotonin neurons are localized from the caudal part of the midbrain red nucleus to the decussation of the pyramid of the medulla. This pattern is similar among species. Approximately 65% of the cell bodies are localized near the raphe nuclei group at the center of the brain stem, including the dorsal raphe nucleus (B7), superior central nucleus (B8), pontine raphe nucleus (B5), raphe magnus nucleus (B3), obscurus raphe nucleus (B2), and raphe pallidus nucleus (B1) from the rostral side, while the remaining cell bodies are localized at other sites. Serotonin neurons number between 25-50,000 in rodents and $\geq$150,000 in primates (monkeys), and the B7 group accounts for a large proportion of the serotonin neurons (Nieuwenhuys, 1985; Takeuchi, 1988).

2.2 Serotonin fiber distribution

Axons and dendrites of serotonin neurons are distributed more densely and widely than previously predicted in the central nervous system. The density and area of their distribution exceed those of the noradrenalin neuron system. The distribution of serotonergic axons and dendrites differs markedly between species. This tendency is most remarkable in the neocortex. The distribution pattern of serotonin fibers in the motor, sensory, and visual cortices of rodents is similar, whereas it differs markedly in the neocortex in primates. These distribution patterns of serotonin fibers are presumed to be dependent on the functions of the neocortex. In general, serotonin fibers are distributed more densely in the granular cell layer in the input system of the cortices than in the pyramidal cell layer in the output system, and the density of serotonin distribution is much higher in the primary visual cortex than in the primary motor cortex in primates. On the other hand, noradrenalin fibers are distributed more densely in the pyramidal cell layer in the output system and the distribution is complementary to that of serotonin fibers, i.e. "mutually exclusive distribution pattern" (Nieuwenhuys, 1985; Takeuchi, 1988).

2.3 Projections to other monoamine neuron systems

The serotonin neuron system regulates the activity of other monoamine neurons, in particular, dopamine neurons. For example, serotonin fibers are distributed in a markedly high density in the substantia nigra, and synapses are formed with a number of dopamine neurons in the substantia nigra in all animal species. Thus, the serotonin neuron system controls dopamine neurons in the substantia nigra at the cell body level via the 5-HT2A receptor. Serotonin fibers are distributed not only at sites rich in dopamine fiber endings, such as the striatum and nucleus accumbens, but also in the prefrontal area of the frontal cortex, which is important for the pathogenesis of developmental disorders.

2.4 High sprouting capability

The serotonin neuron system exhibits a markedly high sprouting capability compared with that of other neuron systems. In general, serotonin fibers are sparsely distributed at the striatum. When the substantia nigra is chemically ablated unilaterally during development (by 12 days after birth in mice) using 6-hydroxydopamine, dopamine neurons in the substantia nigra and dopamine fibers in the striatum disappear. In contrast, axon sprouting of serotonin fibers appears in the striatum of the experimental animals and generates a markedly dense distribution. These findings suggest that the serotonin neuron system has a strong influence on the dopamine neuron system (Yamazoe, 2001). This phenomenon, called "heterotypic sprouting", is observed particularly between the serotonin neuron and dopamine neuron systems. Heterotypic sprouting of serotonin fibers during development is thought to be involved in the plasticity of the brain and the modification of symptoms of diseases derived from dysfunction of the dopamine neuron system. Therefore, heterotypic sprouting is particularly intriguing in investigating the pathogenesis of developmental disorders.

2.5 Volume transmission

As mentioned previously, the serotonin neuron system is called the total control system or the diffuse projection system, and plays a major role in central nervous system function. The conventional projection system is called the "wiring transmission" system, and the serotonin neuron system is thought to be responsible for non-functional ("volume transmission") and junctional neurotransmission (Bunin, 1999).

2.6 Development and the serotonin neuron system

During brain development, serotonin has been shown to influence the maturation of target tissues, including dendritic elaboration, synaptogenesis, neurogenesis and organization of the cortex (Lauder, 1978, 1990; Kondoh, 2004). At early stages of development, when the blood–brain barrier is not yet fully formed, serotonin can enter the brain of a developing fetus, and cause a loss of serotonin terminals through negative feedback. This loss of serotonin innervation persists throughout subsequent development and the symptoms of autism appear (Whitaker-Azmitia, 2005).

Serotonin neurons appear at 5 weeks of gestation and their numbers increase dramatically through the tenth week. Raphe nuclei can be detected at 15 weeks gestation. Axons from serotonin neurons grow into the cortex prenatally and expression of the serotonin transporter begins at the end of the first trimester. Serotonin levels in the brain increase postnatally for 2-5 years, then decline to adult levels at approximately 50% of the peak values (Whitaker-Azmitia, 2005).

In rats, serotonin fibers exhibit a temporary control over the primary sensory cortex during fetal days 2-14, which corresponds to the period of synapse formation. Serotonin transporters appear temporarily in glutamatergic thalamocortical afferent nerve fibers within 2 weeks after birth in rats. Serotonin concentrations that are too high or too low influence normal development during this period (Erzurumlu & Kind, 2001). An insufficient concentration of serotonin in the brain during synapse formation interferes with the development of the barrel in the rat somatosensory area. In contrast, excessive serotonin induces superabundant axonal branching in the somatosensory area and obscures the boundary of the barrel, as observed in monoamine oxydase A-knockout mice (Erzurumlu & Kind, 2001). Abnormalities in synaptic connection induced by a reduced or excess intracerebral serotonin concentration greatly reduces the number of dendrites not only in the sensory cortex, but also in the hippocampus. Considering that serotonin fibers are densely distributed in the granular cell layer in the cerebral neocortex, polymorphisms of the serotonin transporter gene reported in autism spectrum disorders patients may influence serotonin regulation in the thalamocortical nerve pathway, which may lead to abnormalities in sensory and cognitive functions in most autism spectrum disorders patients.

Development of the serotonin neuron system is influenced by a variety of environmental factors. In mice, studies have shown that malnutrition and hypoxia during the neonatal period induce irreversible changes in the serotonin neuron system, that vulnerability of the serotonin neuron system is dependent on the region, and that a variety of environmental factors may induce brain injury associated with the serotonin neuron system (Ishimura, 1989). Moreover, the serotonin neuron system is influenced greatly by aging, and S100β in astrocytes is involved in the dynamics of serotonin fibers in the hippocampus. Axons originating from the B7 and B8 groups show different intracerebral distribution and degenerative process associated with aging, and each has specific neurobiological significance (Nishimura, 1995). Considering the pathogenesis of autism spectrum disorders, it is of interest that the serotonergic system is activated through rhythmic movements, such as gait, chewing and respiration, and that adequate physical activity is important for serotonin activation (Kohyama, 2011). Thus, accumulating evidence indicates that serotonergic projections undergo continuous age-related change through early childhood and that the serotonin neuron system is particularly plastic and fragile.

3. Serotonergic neurotransmission in autism spectrum disorders

In this review, autistic disorder (Kanner's 'autism'), childhood disintegrative disorder, pervasive development disorder not otherwise specified ('atypical autism'), and Asperger syndrome are collectively termed autism spectrum disorders (Persico & Bourgeron, 2006). According to previous studies, abnormalities in the brain stem-subcortical structure (caudate nucleus, putamen, and pallidum)-cerebellum network, as well as in the hippocampus, piriform gyrus, and cingulate gyrus, play a central role in the pathogenesis. A number of studies have examined the relationship between autism spectrum disorders and abnormalities in the serotonin neuron system, and these abnormalities are considered to be the core of the pathogenesis of autism spectrum disorders (Johnston & Blue, 2006; Persico & Bourgeron, 2006).

3.1 Hyperserotonemia

Increased blood serotonin concentrations in approximately 30% of autism spectrum disorders patients strongly suggests that serotonin is involved with the onset of autism spectrum disorders. Although an increase in serotonin uptake by platelets elevates serotonin concentrations in the blood, an abnormality in the serotonin neuron system has not been identified in these patients. The relationship of blood serotonin to the behavioral aspects of autism spectrum disorders and the range of blood serotonin concentrations in the autism spectrum disorders group are not clear. Serotonin levels have not been correlated consistently with degree of mental retardation or other symptoms (Anderson, 2005). High serotonin levels in the blood have been suggested to cause a low intracerebral serotonin concentration in autism spectrum disorders, and are considered to be the result of negative feedback on serotonin neurons (Whitaker-Azmitia, 2005). This negative feedback is likely mediated by the 5-HT1A, which is the earliest appearing serotonin receptor and has a prenatal peak both in human and rodents. In some cases, the receptor appears transiently during development in brain regions, such as the cerebellum, that do not express the receptor in the adult.

Although most serotonin-related neurochemical research in autism spectrum disorders has focused on hyperserotonemia, several studies examining serotonin in cerebrospinal fluid have been reported (Anderson, 2005). However, cerebrospinal fluid studies are in general agreement that little or no difference exists between the mean levels of the major serotonin metabolite, 5-hydroxyindoleacetic acid in autism spectrum disorders patients and control groups.

3.2 Serotonin hypothesis based on clinical viewpoints

The concept of autism has changed over time. The main symptoms of autism spectrum disorders include onset in early infancy, male predominance, age-dependent symptomatic development, and symptomatic vulnerability to the influence of environmental factors. The neuronal system responsible for these clinical distinctions should have the following characteristics: development in early infancy, predominant vulnerability in males, involvement in the regulation of the growth and function of the brain by projecting to the subcortical to cortical levels, and susceptibility to environmental factors. These features suggest that a brainstem monoamine neuron system may be the primary contributor to the pathogenesis of autism spectrum disorders. Among them, the serotonin neuron system is considered the most favored candidate since it fulfills all of the characteristics outlined above (Segawa & Nomura 2005). Abnormalities in the serotonin neuron system are thought to cause disturbances in the sleep/arousal rhythm observed from the early stages of autism

spectrum disorders, poor social skills, adaptation disorder to a new environment, and impaired cognitive function.

3.3 Positron emission tomography studies

Analysis of serotonin metabolism by positron emission tomography (PET) revealed that serotonin synthesis is disturbed in the frontal lobe, thalamus, and cerebellum, which are thought to be involved in the pathogenesis of autism spectrum disorders. PET using α [C-11] methyl-L-tryptophan showed that the uptake of α [C-11] methyl-L-tryptophan in autism spectrum disorders is different between the right and left sides in the frontal lobe, thalamus, and cerebellar dentate nucleus. When compared with the adult levels of serotonin synthesis in the whole brain, the level of serotonin synthesis in children up to five years old without autism spectrum disorders was $\geq$200% that of adults, and gradually decreased thereafter to the level in adults. The serotonin synthesis levels decreased earlier in female children than in male children. However, in children with autism spectrum disorders, serotonin synthesis gradually increased from 2 to 15 years old to a level 1.5-fold that of the adult (Chugani, 1999; Chugani, 2002). PET studies using [11C](+)McN5652, which is highly selective for the serotonin transporter, as a tracer showed that serotonin transporter density in Asperger syndrome patients was significantly decreased in a wide area containing the midbrain, basal ganglia, and cerebral cortex. These results need to be verified fully.

3.4 Neuropathologic changes implicating the serotonin neuron system

Most regions of the brain reported to be responsible for autism receive rich projections from the serotonin neuron system pathologically, in that they have dense serotonergic terminals. Thus, abnormalities in serotonin neurotransmission may be involved in the pathogenesis of autism spectrum disorders. To date, potential foci responsible for autism spectrum disorders have been reported, including the superior and inferior olivary nuclei, facial nerve nucleus, dorsal raphe nucleus in the brain stem, the frontal lobe (prefrontal area) and lateral lobe (superior temporal gyrus) in the cerebral cortex, cerebellar vermis and hemispheres, and the cingulate gyrus, septal area, amygdala, and hippocampus in the cerebral limbic system (Amaral, 2008). Neuropathologic foci of autism spectrum disorders are present widely, suggesting that brain injury occurs at an early stage of development.

In regards to neurotransmission, most of the foci reported to be responsible of autism spectrum disorders are strongly projected by the serotonin neuron system, except for the cerebellum. A particularly strong rationale has been developed for involvement of the amygdala and associated areas of the limbic cortex. More specifically, the core social relatedness deficits in autism spectrum disorders serve to focus attention on the rostral limbic system, including the amygdala, septum, medial orbitofrontal cortex, anterior insular cortex, anterior cinglate cortex, and the nucleus accumbens (Anderson, 2005). The various limbic areas are richly innervated with serotonergic projections, and the nucleus accumbens, an area crucial in appetitive and reward processes, has an especially dense serotonergic innervation. Meanwhile, in the cerebellum, where serotonin fiber density is lower than in most other brain areas, the serotonin neuron system is thought to be crucial for cerebellar function. As described before, 5HT-1A receptors have a rich and early expression in the rodent and human cerebellum. Therefore, neuropathological findings strongly suggest that abnormalities in serotonergic neurotransmission may be involved in the pathogenesis of autism spectrum disorders. Furthermore, neuropathological findings in the brain were compared between reeler mice deficient in reelin and autism spectrum disorders patients,

and common lesion distribution and microscopic findings between the two conditions were observed (Persico & Bourgeron, 2006). In addition, the serotonin agonist, 5-methoxytryptamine, influences the level of reelin, which shows an abnormal level in the brains of autism spectrum disorders patients.

3.5 Animal models of autism spectrum disorders

In animals, serotonin is involved in mediating behaviors of sleep, arousal, aggression, impulsivity, and affiliation, all of which are relevant to autism. Reduced serotonergic function has been associated with worsened sleep, depressed mood, altered arousal, increased aggression, and increased impulsivity (Anderson, 2005). In general, serotonin plays an inhibitory role in the brain. Its actions are complex and depend greatly on the specific location or distribution of serotonergic terminals and classes of receptors stimulated. In regards to animal models for autism spectrum disorders, a thalidomide-administered model (rat), a valproic acid-administered model (rat), a Borna disease virus infection model (rat), an amygdala injury model (monkey, rat), and a hypothyroidism model (rat) have been constructed. A majority of the animal models show abnormal early development of the serotonin neuron system, although abnormalities in the dopamine and noradrenalin neuron systems have also been suggested. Furthermore, as in the autism spectrum disorders animal models, oxytocin-deficient and oxytocin receptor-deficient mice have been reported.

3.6 Other models related to serotonin

The involvement of the serotonin neuron system in the pathogenesis of autism spectrum disorders has been reported from a variety of fields. (1) A mutation in the tryptophan 2,3-dioxygenase gene that encodes the rate-limiting enzyme in tryptophan-serotonin-kynurenine metabolism was reported in autism spectrum disorders patients. (2) Serotonin depletion during the neonatal period increased the thickness of the cerebral cortex, which is a common finding with an increased cerebral volume in autism spectrum disorders patients. (3) 5-methoxytryptamine has been shown to influence the level of reelin, which shows an abnormal level in the brain in autism spectrum disorders patients (Janusonis, 2004). (4) A selective serotonin reuptake inhibitor was shown to improve clinical symptoms. However, the factors that may critically affect the response to selective serotonin reuptake inhibitor treatment and adverse effects in individuals with autism spectrum disorders need to be clarified. (5) Risperidone, another frequently used medication for patients with autism spectrum disorders, is an atypical neuroleptic that acts as a potent antagonist at the 5-HT2A receptor.

3.7 Oxytocin and autism spectrum disorders

Oxytocin is a peptide hormone produced by neurosecretory cells at the hypothalamus supraoptic nucleus and paraventricular nucleus in mothers and it is secreted from the posterior pituitary lobe. The hormone exhibits a variety of functions in the brain, as well as roles in delivery and galactopoiesis. Oxytocin regulates emotion in the company of somebody and oxytocin concentrations in the blood are low in autism spectrum disorders patients, therefore, the hormone attracts the most attention in investigations of the pathogenesis of autism spectrum disorders (Kirsch. et al; 2005). Oxytocin plays a role in signal transmission between the mother and the fetus so that neurons in the fetus are prepared for delivery. Oxytocin temporarily switches intracerebral GABAergic neurotransmission from the excitatory to inhibitory state in the fetus at delivery and exerts

neuroprotective action. Serotonin fiber endings are abundant on oxytocin neurons at the hypothalamus supraoptic nucleus and paraventricular nucleus, and it should be noted that oxytocin neurons are regulated by the serotonin neuron system.
Studies to date show that prenatal treatment with a serotonin agonist, 5-methoxytryptame, results in "autistic-like" behaviors such as decreased social bonding, sensory hyper-responsiveness, seizures and motor changes (Whitaker-Azmitia, 2005). 5-methoxytryptame (serotonin agonist)-treated animals have a loss of oxytocin-containing cells in the hypothalamus, as well as an apparent loss of oxytocin projections towards other brain regions such as the amygdala and the supraoptic nucleus. The amygdala is of interest in autism spectrum disorders because there have been reported changes in volume, cell-packing density and function in this region. In addition, the central nucleus of the amygdala receives an intense serotonergic innervation from the dorsal raphe nucleus, which may modulate behavioral responses to fear (Adolphs, 2002).

3.8 Glutamic acid, neuroligin, and neurexin in autism spectrum disorders

Glutamic acid, as well as serotonin plays an important role in the development of the brain. Glutamic acid is essential for the development and plasticity of the cerebral cortex, and is responsible for the collaborative function with serotonin in the development of the thalamo-cortical pathway. In the cerebellum in autism spectrum disorders patients, up regulation of the glutamate receptor 1 subunit of AMPA mRNA has been reported. In addition, genetic mutations in neuroligin-3 and 4 genes result in changes in glutamatergic synapses. Furthermore, as it has been shown that the balance between excitatory and inhibitory neurotransmission is disturbed by the down-regulation of neuroligin-1, shifting to the excitatory side. Synapse dynamics such as plasticity, production, and pruning is impaired; therefore, the importance of glutamic acid in autism spectrum disorders has been suggested (Johnston & Blue, 2006). Neuroligin and neurexin are cell adhesion molecules located at the postsynaptic and presynaptic region, respectively. They promote synapse formation bidirectionally in the glutamatergic nerve system and GABAergic nerve system, and they have been called "the bridge between molecules and the mind" (Dean & Dresbach, 2006). Insufficient inhibitory neurotransmission is related to impaired cognitive processes, physical control, and the tendency to be complicated with abnormal brain waves and epilepsy in autism spectrum disorders. While mutated proteins of neuroligin 3, neuroligin 4, and neurexin 1 have been reported in autism spectrum disorders patients, the involvement of neuroligin 4 in attention-deficit hyperactivity disorder and learning disorder has also been suggested (Dean & Dresbach, 2006; Betancur, 2009).

3.9 Autism spectrum disorders-related proteins

Autism spectrum disorders-related proteins have a variety of functions including remodeling of chromatin and transcription regulation, the actin cell cytoskeleton, the induction and maintenance of dendritic spines, neurotransmission (neurotransmitters, receptors, and transporters), as a second messenger, apoptosis, cell adhesion, and nerve cell mobilization (Persico & Bourgeron, 2006). SLC6A4, which encodes the serotonin transporter, has been intensively investigated as an autism spectrum disorders-related gene. In addition, genes encoding a GABA receptor subunit (GABAR: GABRA4 and GABRB1), an NMDA receptor subunit (GRIN2A), the oxytocin receptor (OCTR), and the vasopressin receptor (AVPR1) have also been investigated as autism spectrum disorders-related.

4. Serotonergic neurotransmission in attention deficit hyperactivity disorder symptoms in patients with autism spectrum disorders

The majority of the patients with autism spectrum disorders are diagnosed as having attention deficit hyperactivity disorder at an early stage of the disease, suggesting a common neuronal dysfunction between attention deficit hyperactivity disorder and autism spectrum disorders. Attention deficit hyperactivity disorder is a disease that involves a number of genetic factors. It is a heterogeneous disorder with a wide variation in symptoms among individuals, and is influenced by environmental factors. Dysfunction in the catecholaminergic (dopaminergic and noradrenergic) system in the neocortex (prefrontal area)-subcortical structure (the caudate nucleus, putamen, pallidum, and thalamus)-cerebellum pathway is the core of the pathogenesis of attention deficit hyperactivity disorder. The serotonin neuron system is related not only with the abnormality in the catecholaminergic system, but also directly with the pathogenesis of attention deficit hyperactivity disorder (Biederman, 2005).

4.1 Dopaminergic neurotransmission in attention deficit hyperactivity disorder

It is generally accepted that abnormalities in the dopaminergic system are the core of the pathogenesis of attention deficit hyperactivity disorder. Among monoamines, dopamine is located profusely in the brain. The dopaminergic system is also considered a diffuse projection system, however, the distribution is relatively localized compared with the serotonergic and noradrenergic systems. The cell bodies of the dopamine neuron system are distributed in a concentrated manner at the midbrain substantia nigra pars compacta and ventral tegmental area. Dopamine neurons are also localized in the mesocorticolimbic dopaminergic pathway, which has projections to the ventral tegmental area, accumbens nucleus, amygdala, septal area, olfactory tubercule, and prefrontal area, and is deeply involved in functions such as motivation, sustained attention, cognitive function, and reward behavior (Björklund & Dunnett 2007).

A dopamine transporter, localized at the cell membrane, plays an important role in dopamine metabolism by incorporating extracellular dopamine into the cell and decreasing extracellular dopamine concentrations. Single photon emission computed tomography with the administration of altropane, which binds the dopamine transporter specifically, showed that the binding capacity of ^{123}I altropane in the striatum increased by 70% in adults with attention deficit hyperactivity disorder, suggesting the over expression of the dopamine transporter in attention deficit hyperactivity disorder.

After methylphenidate was administered for 4 weeks in the treatment for attention deficit hyperactivity disorder adults, single photon emission computed tomography showed that dopamine transporter activity in the striatum, which was higher than that in the control group before treatment, decreased after treatment and showed no significant difference from controls. The normalization of dopaminergic neurotransmission confirmed the clinical effect of methylphenidate. Furthermore, positron emission tomography with C^{11}altropanea was carried out for a comparative experiment that took into account a history of medication and smoking, and the results showed that the dopamine transporter was significantly increased at the caudate nucleus (on the right) in adult attention deficit hyperactivity disorder cases. Therefore, deregulation of the dopamine transporter resulted in attention deficit hyperactivity disorder (Spencer, 2007). These findings are consistent with the hypothesis that the striatum is involved in the regulation of complicated cognitive function and that the putamen is involved mostly in the control of physical function.

The over-expression of the dopamine transporter in the striatum in humans was confirmed by a number of studies using single photon emission computed tomography and positron emission tomography, but examinations of a bilateral difference of the dopamine transporter in the striatum are not consistent. The distribution of the dopamine transporter is greatly dependent on site, and distribution density is much higher in the striatum than in the frontal lobe, which is known to have the dopaminergic system at the highest density in the cerebral cortex (Stahl, 2008).

As described previously, the monoamine system is responsible for not only conventional neurotransmission via synapses, but also volume transmission without the involvement of synapses. Dopamine carries out neurotransmission in a wide area in the prefrontal area by spreading to the outside of synapses, as well as synaptic clefts, and it is involved in frontal cortex functions, such as selective attention at the dorsal anterior cingulate gyrus, sustained attention in the dorsal lateral prefrontal area, regulation of hyperkinesias in the premotor cortex, and impulsivity control in the orbitofrontal cortex.

4.2 Serotonergic neurotransmission in attention deficit hyperactivity disorder

4.2.1 Interaction between dopaminergic and serotonergic systems

Previous studies of the dopaminergic system in the mesocorticolimbic pathway in attention deficit hyperactivity disorder model rats have demonstrated a loss of function in 6-hydroxydopamine rats, a loss of function and gain of function in spontaneously hypertensive rats, and a gain of function in dopamine transporter knockout/knock-down mice. The anatomical characteristics of the serotonin neuron system suggest a mechanism for disinhibition of the dopaminergic system in association with loss of function in the serotonergic system. Therefore, it is highly likely that abnormalities not only in the dopaminergic system, but also in the serotonergic system are involved in the pathogenesis of attention deficit hyperactivity disorder.

When 6-hydroxydopamine is administered to neonatal rats, they show hyperkinesias for a specific period after birth. In this model, 6-hydroxydopamine destroyed dopaminergic fibers in the prefrontal area and striatum, and dysfunction of the dopaminergic system or the ensuing dopamine receptor hypersensitivity is considered the underlying mechanism for hyperkinesias. Serotonin fiber density is increased remarkably in the striatum of these 6-hydroxydopamine model rats and mice. It has been reported that the excessive control of the serotonergic system is involved in the inhibition of hyperkinesias by a central nervous system stimulant. The delicate balance between the dopaminergic and serotonergic systems is thought to be necessary for normal behavior and monoamines are likely involved in heterogeneity (sub-classification) of attention deficit hyperactivity disorder. In general, when this disorder in the dopaminergic system is predominant, destructive and aggressive behavior is less frequent, and hyperkinesias and attention deficit are the chief complaints of attention deficit hyperactivity disorder. However, when impairment in the serotonergic system is predominant, not only hyperkinesias and attention deficit, but also destructive and aggressive behavior are observed in attention deficit hyperactivity disorder.

4.2.2 Direct involvement of the serotonergic system in attention deficit hyperactivity disorder

Dopamine transporter knockout mice are known as an attention deficit hyperactivity disorder animal model. The administration of methylphenidate alleviates the hyperkinesias in dopamine transporter knockout mice. However, since dopamine transporter, a target of

methylphenidate, is deficient in this mouse model, it is reasonable to conclude that the effect is exerted via other neuron systems. When a serotonin transporter inhibitor (a selective serotonin reuptake inhibitor) is administered in this mouse model, hyperkinesias are alleviated despite no change in extracellular dopamine concentrations (Gainetdinov, 1999). On the other hand, when a selective noradrenalin transporter inhibitor (a selective noradrenalin reuptake inhibitor) is administered, hyperkinesias are not alleviated, which suggests that serotonergic neurotransmission is involved in the functional mechanism of methylphenidate for the improvement in attention deficit hyperactivity disorder symptoms.
The serotonergic system per se is directly involved in attention deficit hyperactivity disorder and is involved mostly in sustained attention, particularly in the dorsal lateral prefrontal area. Recently, serotonin at the dorsal striatum and prefrontal area has been suggested to play an important role in inhibiting impulsivity in decision-making and aggressiveness (Doya, 2008).
Selective serotonin reuptake inhibitors improve attention deficit hyperactivity disorder symptoms via the 5-HT1A, 5-HT2A, and 5-HT2C receptors. Since 5-HT1B receptor-deficient mice show hyperkinesias and aggressiveness, the 5-HT1B receptor has attracted attention as a genetic factor of attention deficit hyperactivity disorder, and the relationship between the subtypes of attention deficit hyperactivity disorder and the attention deficit-predominant type has also been examined (Smoller, 2006).

5. Conclusions

Serotonin is the earliest developing neurotransmitter system in the mammalian brain, and eventually becomes the mostly widely distributed system in the brain, contacting most cells of the cortex. Thus, the serotonin neuron system develops early enough, and is sufficiently widespread that it can influence maturation of many other regions in the brain. The serotonin neuron system that develops at the early stage has a core influence on neural development, morphogenesis, and synapse formation and maintenance. The control of the serotonin neuron system over other monoamine neurons, in particular, dopamine neurons, has been demonstrated. These neuroanatomical findings are important for understanding the pathogenesis of developmental disorders.
In autism spectrum disorders, abnormalities in the brain stem-subcortical structure (caudate nucleus, putamen, and pallidum)-cerebellum network, as well as the hippocampus, piriform gyrus, and cingulate gyrus, plays a central role in the pathogenesis. Since most parts of the brain that have been reported to be responsible for autism spectrum disorders strongly receive projections from the serotonin neuron system, dysfunction of serotonergic neurotransmission is considered to be the core of the pathogenesis of autism spectrum disorders. Abnormalities in the serotonergic system are thought to cause disturbances in the sleep/arousal rhythm observed from the early stages of autism spectrum disorders, poor social skills, and adaptation disorder to a new environment. Dysfunction in the dopaminergic and noradrenergic systems in the neocortex-subcortical structure-cerebellum pathway is the core of the pathogenesis of attention deficit hyperactivity disorder, and the serotonin neuron system is related not only with the abnormality in the catecholaminergic system, but also directly with the pathogenesis of attention deficit hyperactivity disorder.

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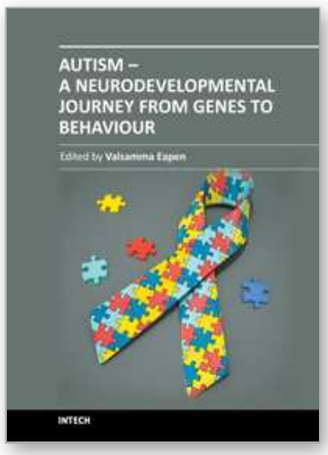

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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