



REVIEW ARTICLE

Cortico-Striatal Pathway Alterations in Autism

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Abstract

The specific neurological mechanisms underlying widespread motor stereotypes and social impairments in autism spectrum disorder (ASD) remain unknown. However, strong evidence supports a genetic influence on ASD. In this work, we analyze the role of corticostriatal pathway dysfunction in a core symptom of ASD.

Keywords

Autism, Costicostriatal pathway, Motor stereotypes, Neurodevelopment, Genetic

Autism Disease Spectrum

ASD is a neurodevelopmental disorder characterized by poor social communication, cognitive deficits, and stereotyped or repetitive behavior (American Psychiatric Association (APA), 2013). Nowadays, the World Health Organization (WHO) considers the international prevalence of this disorder to be about 0.76% and is more common in males [1]. The genetic and environmental influences on autism prevalence, however, an etiologic mechanism have not yet been established. Two characteristic symptoms in autism are stereotyped behavior and social interaction problems and could indicate the severity of the disorder; both might be due to an alteration in cortico-striatal integrity.

Cortico-Striatal Pathway

The dorsal striatum is part of the basal ganglia, including the: caudate nucleus (CN) and putamen (Put). There are two theories about the functioning of the

striatum. The first suggests it is a structure that receives inputs from other areas and funnels the information [2], and the second theory asserts the striatum participates in a segregated parallel circuit (involving all basal ganglia) [3].

Nowadays, we know that the dorsal striatum receives a wide range of input, including extensive glutamatergic innervation from cortical pyramidal neurons by two pathways: the intratelencephalic tract (IT) -ipsi- or bilateral connections- and the pyramidal tract (PT). These pathways are differentiated by molecular signaling and organization. The cortico-striatal IT pathway occurs in neocortical layers 5A, 5B, and 6. The electrophysiology profile in IT neurons shows a prominent hyperpolarization-activated current when compared with pyramidal neurons [4]. Also, the dorsal striatum is a reservoir of monosynaptic excitatory projections from sensory, motor, and limbic cortices [5]. The putamen is primarily involved in motor control due to its connections with the supplementary motor area and premotor cortex in macaque [6]. In addition, the caudate nucleus and the ventral striatum participate in saccadic eye movement and, through their connections with the cingulate cortex, are also important for limbic (emotional) functions [7]. On the other hand, the ventromedial part of the caudate nucleus connects with the orbitofrontal cortex, which is related to the limbic system and modulates functions such as emotion, motivation, and social reward [8,9]. The frontal cortex, specifically the orbitofrontal cortex

(OFC), participates with the striatum in social rewards [10] and social cognition [11]. The caudate's roles in cognitive functions include learning, attention, habit formation, and decision-making, and are carried out by the dorsolateral prefrontal circuit [12,13].

Striatal Neurodevelopment

The neurodevelopmental alteration in the striatum has been widely explored in diseases like Huntington's, Tourette's syndrome, and schizophrenia. These alterations also appear to have a significant relationship with core autism symptoms, namely stereotyped behaviors and impaired social abilities. The more explored is motor behavior.

The formation of the striatum starts at embryonic day 10.5 (E10.5). From E11.25 to approximately E13, the central and peripheral cells start to form the striosome, and by E14.25, the matrix surrounds it [14]. Concerning the cortico-striatal circuit, at E12, the growth cones of corticofugal axons enter the developing striatum, with collateralization occurring at E18-P2 and arborization at P2-P7 [15]. The migration of interneurons starts from the lateral ganglionic eminence (LGE) in mice [16] and from the medial ganglionic eminence (MGE) in humans and monkeys [17].

It has been demonstrated in mice that the striatal afferents act differentially in order to maintain the survival of the striatum's interneurons. During striatum development, there are elevated levels of semaphorin 3A and 3F [18], as well as Nkx2-1 gene participation in the differentiation of GABAergic interneurons and oligodendrocytes [19]. While the absence of Lhx8 protein does not differentiate cholinergic interneurons, it does differentiate GABAergic interneurons [20]. In addition, at P21, the inputs from cortical neurons support the survival of PV+ interneurons; moreover, the medium spiny neuron (MSN) afferents maintain the ChAT+ interneuron survival [21].

Striatum Cytology

The appearance of the striatum is due to the striosomal complex, which was described by [22]. The striatal tissue comprises a vast majority (95%) of medium spiny projection neurons (MSNs), with a low proportion of aspiny GABAergic neurons, as well as interneurons [23]. Interneurons are classified by electrophysiological characteristics: parvalbumin (PV+)-expressing fast-spiking interneurons (FSI), fast-adapting interneurons (FAI), low-threshold spike cells (LTS) [24], spontaneously active bursty interneurons (SABl) [25], and persistent low-threshold spike cells (PLTS) interneurons [26]. Neurochemical classification identifies neurogliaform (NGF) Neuropeptide-Y (NPY) [27] tyrosine hydroxylase (TH), and calretinin (CR) striatal interneurons [28].

Excitation and Inhibition Balance during Neurodevelopment and Molecular Signaling

Striatal connectivity allows this area to function as a gateway for modulating and regulating the excitatory range within the basal ganglia circuit. Medium spiny neurons (MSNs) are the most prominent cell type in the striatum, integrating GABAergic, glutamatergic, dopaminergic, and cholinergic inputs, as well as hormonal sex influences [29,30]. The two main MSN groups are striatonigral and striatopallidal neurons, differentiated by their neurochemical and electrophysiological characteristics. Striatonigral neurons express DR1 and contain neuropeptides NPY and dynorphin, while striatopallidal MSNs express DR2 and contain enkephalin [31,32]. These MSN types also exhibit differences in their electrical properties [33].

Studies on ASD-related genes have indicated an imbalance of neural network excitation/inhibition in the corticostriatal pathway [34]. The striatum receives a wide range input, including extensive glutamatergic innervation from cortical pyramidal neurons and serves as a gateway for excitatory signals to the basal ganglia, while its inhibitory output contributes to motor control. The cortex in ADS often shows hyperactivity [35]. The dysbalance E/I may result from GABA suppression and the excitatory tone enhancement [36]. Additionally, D1 dopamine receptor-dorsal striatum overactivation interacts with the metabotropic glutamate receptor (mGluR5) and increases repetitive movements, among other ADS-symptoms [37]. Glutamatergic input has been proposed to activate interneurons, but also regulate their inhibitory output [38].

Stereotypes and Social Skill Deficits in Autism

The stereotyped movement's forms part of hyperkinetic movements, and are necessary in the first months of post-natal life in order to develop a complex motor behavior in the future [39]. However, extended stereotyped movements occur in several neurological diseases, including ADS [39,40]. The rate of stereotyped movements indicates the severity of the neuropsychiatric condition and could be sex-dependent [41]. A positive correlation has been shown between striatal volume and repetitive movement's scores in adult autistic patients [42]. In an addiction model using monkeys, stereotyped movements that are dopamine-dependent, result from dorsal and ventral striatum activation [43], potentially due to failed connections with the frontal and prefrontal cortex. The striatum also participates in learning social rewards, that can be altered by striatal dysfunction in autism and may be more severe in males [44,45]. D1/D2 receptors participation has been demonstrated in motor stereotypes and abnormal social behavior in mice [46]. A significant number of gene mutation (discussed later)

have been related to stereotyped movements. Then, this maladaptive behavior is the result of aberrant cortico-striatal connections in the dorsal striatum, originating during development and are GABA-dependent [47]. However, the studies about connectivity in cortico-striatal pathway remain controversial [48].

Perinatal Factors in Autism

Environmental factors occurring before birth are associated with increased ASD risk include maternal stress response activation, prenatal exposure to toxins (thalidomide or valproate), viral infection, prematurity, deficient placental function [17,49-51]. Recently, researchers have found a correlation between acetaminophen use during pregnancy and an increased risk for autism [52]. These conditions are related with oxidative stress, which can lead to abnormal development, polymorphism, and epigenetic changes [53,54].

Genes alteration in ADS stereotypes

FMR1 - Fragile mental retardation 1

Fragile mental retardation 1 (FMR1) is a gene located in X chromosome. Polymorphism of CGG triplet repeat in the 5'UTR [55] can cause DNA methylation and deacetylation altered, this failure eliminates the possibility to produce the fragile X mental retardation protein (FMRP) [56]. FMRP participates in function and morphology in neurons [57,58]. Curiously, fragile X mental retardation and ADS share symptoms such as the stereotyped (repetitive) movements, visual contact avoidance and social anxiety [59].

ML - Mixed lineage leukemia (MLL)

Mixed lineage leukemia (MLL) gene encodes H3K4 methyltransferase enzyme that modulates the expression of other genes, including neuronal genes in neurogenesis in postnatal stage [60]. Its participation has been related with neurodevelopment disorders [61,62], including, ADS [63]. The ablation of this gene in striatum, modulates the neuronal function, modifying the locomotion after amphetamines and increasing the anxiety in mice, compared with control group [64].

SHANK - SRC homology 3 (SH3) and multiple ankyrin repeat domain

The SHANK family genes (SHANK 1, SHANK 2, SHANK 3) encodes shank family proteins. The proteins are scaffolding proteins and assemble the protein complex in the postsynaptic density (PSD) in excitatory glutamatergic neurons [65]. Peixoto showed an enhancement in excitatory signalling in cortico-striatal circuit in mice (Shank 3B -/-) during early development [66]. The Shankopathies has been described in autism [67].

GRIN - Glutamate ionotropic receptor NMDA type subunits

Mutations or deletions in GRIN genes can lead to various neurodevelopmental disorders [68]. Mutations in this gene family may cause an imbalance between excitation and inhibition, potentially contributing to autism [69]. On the other hand, NR2A receptor plays a role in cortico-striatal excitatory via in postnatal day (6 or 8 - 12) in mice [70].

NLGN - Neuroligin

The neuroligin family (NLGN1, 2, 3, and 4) consists of postsynaptic cell adhesion proteins involved in synaptic function. The first two members act differentially at excitatory synapses (NLGN1) and inhibitory synapses (NLGN2). NLGN3 is expressed in both excitatory and inhibitory neurons, while NLGN4 is involved in autism [71-74]. Mutations in NLGN4 produce persistent repetitive movements and abnormal social interaction [75].

DR - Dopamine Receptor

The dopamine receptor D3 gene has been associated with altered striatal volume and stereotyped movements in autism [76].

TSHZ3 - tea shirt zinc finger homeobox family members 3

This gene encodes a protein with the same name, and was initially discovered for regulates smooth muscle cell differentiation during development [77,78] that could be related with caspases regulation. Deletion of this gene results in autism-like behavior and striatal abnormalities [78].

CHD8 - Chromodomain - Helicase DNA binding protein 8

The Chd8 is an ATP-dependent chromatin remodelling factor and regulates the expression of many genes such as Snf2 [79]. In neurodevelopment, this gene has been involved with high neuron proliferation in development causing macrocephaly, among other effects [80]. In the nucleus accumbens (NAc) of mice, the reduction of Chd8 caused macrocephaly, anxiety, social deficiencies, and enhanced motor learning; however, it did not affect repetitive or stereotyped movements [81].

DYRK1A Dual - specificity tyrosine - (Y)-phosphorylation - regulated kinase 1 A

Studies have shown that DYRK1A participates in neuronal proliferation. Its overexpression can block corticogenesis during the embryonic stage (E14.5) [82]. Interestingly, DYRK1A haploinsufficiency altered the proportion of cortical excitatory neurons and caused seizures and stereotyped behavior in mice [83].

EIF4E - Eukaryotic Translation Initiation Factor 4E

The EIF4E complex binds to the 5' cap structure of RNAs and facilitates the export of signaling molecules from the nucleus. Recent studies suggest that EIF4E expression may play a role in autism spectrum disorder (ASD) [84]. EIF4E's involvement in ASD may involve glutamatergic signaling between the prefrontal cortex and the striatum [85]. Conversely, deletion of the EIF4E-binding protein 2 (EIF4EBP2), a suppressor of translation initiation, modulates the imbalance between excitatory and inhibitory signaling, which may be a contributing factor in autism [86]. Both EIF4E and EIF4EBP2 have been linked to repetitive or stereotyped movements in autism [84].

Conclusion

This work explores the potential relationship between the striatum's role in motor functions and social dysfunction. Disruptions in excitatory homeostasis within the striatum may contribute to both stereotyped movements and alteration in social abilities. We review genes associated with corticostriatal pathway alterations as potential targets for mitigating these symptoms in autism.

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