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Landscape of Autism Spectrum Disorders

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Abstract

Autism spectrum disorders (ASD) is a set of neurodevelopmental disorders that is among the most severe in terms of prevalence, morbidity and impact to the society. It is characterized by complex behavioural phenotype and deficit in both social and cognitive functions. This review reports the prevailing theories involved in ASD pathogenesis, including excitatory/inhibitory imbalance, neurotransmitter dysfunction, oxidative stress, effects of mirror neurone dysfunctions, neuro inflammation and immune dysfunction. Despite growing evidence for the involvement of endogenous biomarkers in the pathophysiology of ASD the drug development for ASD management or cure is still in an undeveloped stage. Present review provides some idea towards the possible mechanism of ASD development so by manipulating immune dysfunctions or by inhibiting the neuroinflammation/oxidative stress and also by managing the balance between the levels of various neurotransmitters and excitatory/inhibitory impulse conduction, we can manage or prevent the onset of ASD. Future research can also be devoted on mirror neurones, its impairment repairing so that a new therapeutic target can be identified, by the way we can develop an effective treatment strategy for ASD.

Keywords:*Autism spectrum disorders, Neuro inflammation, Oxidative stress*

LANDSCAPE OF AUTISM SPECTRUM DISORDERS

Autism spectrum disorders are neuro developmental disorders characterized by dysfunctional immune function, stereotypic behaviour and various degrees of impairments in social skills and verbal communication (i.e., language delays)[1].ASD affects almost 1 in 59children [2]. Several forms of ASD have been described, such as Asperger syndrome [3] or Kanner-type autism [4] revealing that ASD is a highly heterogeneous disorder likely with multiple underlying causes. Other neurological and medical conditions frequently co-occur with autism, including mental retardation (30% of cases score mild to moderate, and 40% score serious to profound retardation) and epilepsy (40% of cases)[5]. Co-morbid behavioural and psychiatric conditions associated with the core symptoms include aggression, disruption, hyperactivity, self-injury, sensory abnormalities, anxiety, depression and sleeping disturbances. The most frequent non-neurological comorbidities associated with ASD are gastrointestinal abnormalities and underlying inflammation [6-12], feeding difficulties and food sensitivities [13]. Autistic symptoms normally appear before 36 months of age, and regression or loss of skills occurs in 30% of affected children, usually between 18 and 24 months [14].

Intense scientific work has been performed in recent years to understand the potential origin of ASD, Here, in this review the prevailing theories of ASD pathogenesis, including excitatory/inhibitory imbalance, neurotransmitter dysfunction, oxidative stress, effects of mirror neurone dysfunctions, neuro inflammation and immune dysfunction. Many study results revealing that this disorder arises from both genetic and environmental factors, especially those influencing fetal and early-life development [15].

The Excitatory/Inhibitory Imbalance Theory

The E/I imbalance theory is based on the observation that there are higher incidences of epilepsy and abnormal GABAergic function in patients with ASD. The theory proposes that a loss of inhibitory control may cause elevated noise in the brain's networks and this alters sensory, emotional and social information processing, which in turn reduces the adaptive ability of ASD patients to process and respond to environmental stimulation [16]. This theory further postulated that an increased E/I ratio might be a pathogenic mechanism for ASD. Supporting evidence has come from clinical and genetic mouse model studies that have shown a disruption of E/I homeostasis may result from defective GABAergic inhibitory input, abnormal glutamatergic transmission and/or homeostatic compensation [17]. In ASD models involving maternal valproic acid (VPA) treatment, NMDA receptor (NMDAR)-mediated currents are increased in the medial prefrontal cortex (mPFC) in maternal VPA-treated rats [18-19]. Therefore, an E/I imbalance would seem to be involved in the pathogenesis of ASD-like phenotypes that are induced by VPA. Based on the E/I imbalance theory, several VPA-induced ASD model studies have tested whether activity-dependent manipulation via glutamate receptors is beneficial and able to alleviate ASD-like phenotypes. Clinical studies have shown that genetic mutation of the GRIA2 and GRIA3 subunits of AMPA receptors (AMPAR), are associated with ASD [20-21]. In VPA model systems, GluA1 protein levels and mEPSC amplitudes are increased in the mPFC of VPA-treated mice; furthermore, AMPA antagonist treatment is able to improve the social deficits present in VPA-exposed mice [22]. Along with this, de novo mutation of GRIN2B, a subunit of the NMDAR, has also been found in patients with ASD [23-24]. Based on these findings, NMDAR antagonists have been tested as potential drugs for alleviating the ASD-like phenotypes of VPA-treated rodent offspring. A reduction in the threshold for electronic shock seizure in VPA-treated offspring has been found and this mimics the higher susceptibility of epilepsy in ASD patients. The NMDAR blockers MK-801 and agmatine increase the threshold of electronic shock seizure of VPA-treated rats [25]. NMDA antagonists, including MK-801, agmatine and memantine, relieve the

hyperactivity, anxiety, social impairments and the repetitive behavior of VPA-treated rats [26-27]. In addition to ionotropic glutamate receptors, metabotropic glutamate receptors (mGluR) have also been implicated in ASD pathogenesis. For example, hyperfunction and hypofunction of mGluR5 signaling is known to be involved in Fragile X syndrome and tuberous sclerosis complex (TSC), respectively [28].ASD-like phenotypes induced by the Fmr1mutation, a gene responsible for Fragile X syndrome, are able to be alleviated by administration of mGluR antagonists in mouse models [29-30].However, it is still not very well known how these synaptic inputs influence neuronal circuitry and social behaviour. More comprehensive behavioural and electrophysiological studies need to be done to help better define the role of inhibitory and excitatory transmission in cognitive and social functions.

Neurotransmitters Dysfunction in ASD

Abnormalities of the various monoaminergic systems, including serotonin, catecholamine and histamine, have been observed in ASD patients [30-32].Serotonin (5-hydroxytryptamine, 5-HT) is a neurotransmitter known to be involved in regulating psychiatric function. Hyperserotonemia was first detected in early onsets infantile ASD children, but six out of 23 of the ASD children with highest 5-HT levels were reported in this study to not show specifically correlated clinical signs [33].Elevated levels of blood 5-HT have been reported by a meta-analysis study to be present in 25.4% of ASD patients [31].However, neuropathological studies of human ASD postmortem brains are not consistent with clinical studies. Azmitia et al. (2011) reported that the number of SERT-immunoreactive axons is increased in the 5-HT fibers innervating the cortex and forebrain of ASD brains [34].On the other hand, Oblak et al. (2013) showed that there were significant reductions in SERT, 5-HT receptor 1A (5-HT1A receptor) and 5-HT receptor 2A (5-HT2A receptor) in the posterior cingulate cortex and fusiform gyrus of human ASD postmortem brains; these two cortical regions are involved in social-emotional processing [35]. In addition, genetic linkage studies have identified variants of the SERT gene, SLC6A4, as being present in autistic patients, and that this was found to be correlated with impaired social communication by the ASD patients [36-37].Notably, ASD patients with short-term depletion of tryptophan show deteriorated repetitive behavior and a poorer anxiety status [38]which suggests that a dysregulation in serotonin function is a risk factor for ASD [39]Serotonin is a precursor of melatonin, which is produced in the pineal gland and is involved in the regulation of circadian rhythms [40].Melatonin is relevant to ASD because there is a high prevalence of sleep disturbance among ASD patients [41-42].Abnormal melatonin biosynthesis and reduced levels of melatonin have been found in children and adults who are ASD patients [43-45].Treatment with melatonin is able to reduce such sleep disturbance as well as autistic behavior among ASD individuals [40].

Early research pointing to catecholamine dysfunction in ASD patients is based on the finding that in ASD patients there are increased plasma levels of norepinephrine and decreased plasma dopamine-βhydroxylase activity levels, the latter being the enzyme that converts dopamine to norepinephrine [30].Genetic mutation of the regulators of dopaminergic neurotransmission have been identified as present in ASD patients [44] and these include DRD1,DRD2, [45]DRD3, [46] DRD4 [47] and DAT [48-49]. Notably, the midbrain dopamine systems seem to be involved in the pathology of autism. The dopaminergic mesolimbic and mesocortical pathways have been shown to participate in the reward circuits associated with social motivation and social interaction [50-51]. Reduced dopamine levels in the mPFC of medication-free ASD children, as measured by positron emission tomographic scanning, suggest that hypofunction of the dopamine reward system may be involved in the social communication deficits of ASD patients [52].

The histaminergic system is believed to play an important role in regulating a variety of physiological function; these include the sleep/awake cycle, addiction, neuroinflammation, endocrine control, emotion, learning, and memory [53].Wright et al. (2017) found increased levels of HNMT and three types of histaminergic receptors (H1R-H3R) in postmortem dorsolateral prefrontal cortex of ASD patients' brains [32]. It is noteworthythatGi-coupledH3Risknowntobeabletoindirectly regulate the other neurotransmitter systems that are involved in ASD pathophysiology owing to the fact that this protein can function as both an autoreceptor and a heteroreceptor. This means that it brings about an inhibition of histamine synthesis and the release of other neurotransmitters, respectively. These properties make H3R a potential therapeutic target for the treatment of related cognitive disorders [54-55].

Oxidative Stress and ASD

Oxidative stress is a process by which the body responds to infectious or other invaders through the production of free radicals. When oxidative stress is excessive or chronic and/or when insufficient antioxidants are present, free radicals can result in damage to cell walls and to DNA. Oxidative stress also can have negative effects on the functioning of brain glial cells. Glial cells provide nourishment to neurons and clean up toxic metabolic byproducts such as glutamate. When glial cell function is poor, these functions are disrupted, with negative effects on brain function. Increased GABA is needed to counteract the excess glutamate. When imbalances persist, clinical consequences can include poor language, poor sensory processing, and overall suboptimal brain function [56].Excessive oxidative stress has been described in autism [57]. Inflammation of both intestine and brain is well documented in a subset of individuals with autism. Findings analogous to inflammatory bowel disease are present in some individuals [58].Autopsy studies have documented low-grade chronic inflammation in the brains of individuals with autism [59-60]. Inflammation is one contributing factor to excessive oxidative stress [61].

ImmunologicalDysfunction and Neuroinflammation in ASD

Both innate and adaptive branches of the immune system can impact neural development, cognitive functions, and behavioral pattern. From fetal development to adulthood, the immune system and central nervous system (CNS) interact with each other, influencing both systemic immune response (peripheral immune system) and local CNS immune function (the so-called 'neuroimmunity') [62]. During fetal development, the activation of the maternal immune system may lead to changes in neural development; this is an important risk factor for ASD [63].In the recent years, studies increasingly indicate a strong inflammatory state associated with ASD [64]. This inflammatory condition is often linked to immune system dysfunction [65]. Enhanced inflammatory activity in ASD children has been demonstrated through pro-inflammatory biomarkers [66].Various interrelated factors may cause dysregulation of the maternal immune system. A study conducted by Zerbo et al. [67] found that maternal infectious diseases diagnosed at a hospital admission, especially bacterial ones, were related to increased risk of ASD. Infections during pregnancy, such as rubella [68-70] or influenza virus [71], can create an inflammatory immune environment and trigger the production of maternal cytokines and chemokines, which can not only affect directly the placenta but also may cross the placenta, and enter in the fetal compartment, exerting effects on the fetus development [72].These effects can also be achieved in the absence of active infection, via generalized inflammatory response or loss of immune regulation [73]. In addition, several studies have demonstrated that up to about 10% of mothers with ASD children and only 0–2% of controls have humoral antibodies against fetal brain proteins [62,74-76]. These antibrain auto-antibodies can likewise gain access to the developing fetal brain and bind to fetal proteins, thereby impairing the course of neurodevelopment. Human leukocyte antigen (HLA) genes on chromosome 6 and killer-cell immunoglobulin-like receptor (KIR) genes on chromosome 19 are two large multigene complexes interacting to eliminate unwanted virally infected and malignant cells, and seem to be linked to the risk of developing ASD [77]. Data suggest that HLA alleles and KIR activating genes/haplotypes are common variants in different autism populations [77-79]. At the uterine maternal/fetal interface, maternal NK-cells express leukocyte associated immunoglobulin-like receptor (LAIR) and KIR molecules; they interact with HLA-G non classical molecules expressed on trophoblast cells during pregnancy to suppress normal immune responses [79].Although ASD is not a classical immune mediated disorder, there is an increasing interest in investigating the role of the immune system and inflammation in the development and persistence of the complex neurological and behavioral abnormalities related to ASD [80-82].

The recent demonstration that microglia, the resident immune cells of the central nervous system (CNS), contribute not only to inflammatory events but also to neural development, has raised new hypotheses regarding their role in the etiology of autism. In addition to altered systemic immunity, [83-84] neuroinflammation has been observed in the brain of ASD patients. The presence of activated microglia has been reported in the dorsolateral prefrontal cortex of autistic patients [85] Moreover, Positron Emission Tomography (PET) imaging studies have revealed an activation of microglia in other brain regions [86-87]. Postmortem studies of individuals with ASD have also shown activation of microglia, as well as an increase in density [85,88-89]. Reinforcing the idea of immunological dysfunction in ASD,[90-94] this activation of microglia is accompanied by increased expression of pro-inflammatory factors, such as cytokines and chemokines, in the brain and cerebrospinal fluid of ASD subjects [85,89].Literature data strongly suggest that individuals with ASD differ in immune profile and markers, especially in the pro-inflammatory ones, from healthy individuals or those without ASD. Abnormal interplay between innate and adaptive immunity and CNS in ASD, leading to chronic low-grade inflammation in the CNS, has been reported [95-98]. Lower percentage of CD4 T lymphocytes, skewed CD4:CD8 T cell ratio (31) and, more recently, altered function of T regulatory cells and NK cells have been found in ASD patients [99-101].Additionally, aberrant expression of many pro-inflammatory cytokines and chemokines, such as inteleukin-1(IL-1), interleukin-6 (IL-6), interleukin8 (IL-8) and interleukin (IL-12), as well as macrophage migration inhibitory factor (MIF) and platelet derived growth factor (PDGF) has been demonstrated in ASD patients in peripheral blood, cerebrospinal fluid or brain tissues,[102] and gastrointestinal system [102-104]. Nonetheless, the results are still in conclusive. Saresella et al. [105] suggested the existence of an "autism endophenotype" that expands immune aberrations to relatives who are seemingly unaffected by the core symptoms of ASD, but present autistic traits, including delayed verbal, cognitive, and motor development. They showed systemic immunologic dysfunction in ASD children, such as the augmentation of pro-inflammatory and interleukin10–producing immune cells, the increase of CD8+ naïve T lymphocytes, and the reduction of CD8+ effector memory and CD4+ terminally differentiated; similar immune dysregulation was also observed in related, unaffected siblings of autistic children, but not in healthy control subjects. Other studies further support evidence of a disturbed immune system with altered cytokine levels in ASD children compared with related or unrelated siblings [106-108].However, a significant association of cytokine levels – especially IL-1- with the quantitative traits and the clinical subgroups of ASD was found, confirming the impact of immune alterations on the core symptoms of ASD.

Mirror neurons and ASD

The existence of mirror neurons discovery was happened accidently by Rizzolati et al. [109]These researchers were studying electrical signals of a certain kind of motor neuron in monkeys, and realized, accidentally, that their motor neuron discharged not only when they performed

and action, but also when they saw another monkey or one of the researchers performing the same action [110]. Another researcher Ramachandran states that these neurons are essential to the human being because they can deduct intentions [111]. According to him, these neurons enable the imitation of other people's actions and, therefore, are seen as the "empathy neurons". The mirror neuron system enables individual to understand the action of others, and facilitates social cognitive functions such as empathy and emotional state [112].According to Williams, impairment of the mirror neuron system can affect imitation, producing a constellation of symptoms which characterize ASD [113].Evidence for this came from several studies carried out to confirm the role of mirror neurone dysfunctions were based in functional magnetic resonance imaging studies, [114-115] that is a technique for measuring brain activity and electroencephalography study monitoring activity of the brain [116-117]. It was shown that the mirror neurone activity is altered in children with ASD and that this dysfunction prevents them from understanding the action of others [118].

Concluding Remarks

Here we have reviewed relevant theories related to ASD pathophysiology. The collective findings of ASD includes excitatory/inhibitory imbalance, neurotransmitter dysfunction, oxidative stress, defective functioning of mirror neurones, neuro inflammation and immune dysfunction, but exact etiology or pathology is still not clearly defined because of this the drug development for ASD management or cure in an undeveloped stage. Present review provides some idea towards the possible mechanism of ASD development so by manipulating immune dysfunctions or by preventing onset of neuroinflammation/oxidative stress and also by managing the balance between the levels of various neurotransmitters and excitatory/inhibitory impulse conduction, we can manage or prevent the onset of ASD. Any agent/drug which can act by either of above said mechanisms may serve as a potent therapeutic agent for ASD. Future research can also be devoted on mirror neurones, its impairment repairing so that a new therapeutic target can be identified, by the way we can develop an effective treatment strategy for ASD.

Conflicts of Interest

There are no Conflicts of Interests

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