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Review

GENE SIGNALLING PATHWAYS, PUTATIVE BIOMARKERS AND HYPOTHETICAL MODULATION IN AUTISM SPECTRUM DISORDERS

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Abstract. Autism spectrum disorder (ASD) is one of the most common neurological disorders, with a ubiquitous increase in prevalence. A theoretical rationale is providing for identifying potentially clinically significant diagnostic biomarkers and opportunities for targeted pharmacological modulation based on current data on gene signaling pathways. This systematic review is based on data from systematic reviews and meta-analyses devoted to the basic aspects of autism spectrum disorder. This has made it possible to outline approaches to syndrome-associated diagnosis and treatment strategies. This article explores integrative pathogenetic mechanisms of ASD, encompassing prenatal viral exposure, alterations in serotonin and oxytocin signaling pathways, regulation of N-methyl-D-aspartate receptors, SHANK proteins, and members of the Solute Carrier protein family. Immune, viral, and metabolic factors, neurotransmitter systems, synaptic proteins and structural regulation, biomarkers, and therapeutic strategies were detected as diagnostic and modulation promising in ASD. The potential of combined modulation involving retinoic acid derivatives, folates, antioxidants, neurotrophins, oxytocin preparations, glycine, and magnesium has been demonstrated, depending on the syndromic manifestation of ASD. A possible role of the rubella virus in prenatal disruption of retinoic acid metabolism and subsequent impairment of neuronal pathway formation has been demonstrated, as well as the specific influence of the COVID-19 virus on the IGF-1 signaling pathway. An association has been proposed between autoimmune activation during impaired neuronal maturation and ferroptosis processes, resulting in decreased ferritin and transferrin levels in children with ASD. Analysis of the literature explores the potential for more selective diagnosis and modulation in ASD using specific biomarkers and to indicate directions for future research.

Keywords: autism spectrum disorder; gene signalling pathways; transferrin; ferritin; serotonin; oxytocin; pharmacological modulation

Introduction

ASD is a complex neurodevelopmental disorder with symptoms of progressive social deficit, repetitive behaviour patterns, and reduced interests [1]. ASD has increased significantly over the last decade from 2.47% to 3.14% in the USA, from 0.11% to 1.53% in the Middle East, and from 1.41% to 2.52% in Australia, with a certain predominance among boys [2, 3]. The latest data indicate an ASD incidence rate of 65 per 10,000 population [4]. The prevalence is approximately 17.7 per 1,000 in pubertal age, males 1 in 55, females 1 in 172 [5]. There has been a significant increase in ASD prevalence globally since 2010, as reported by Australia, the USA, Canada, Oman, Sweden, and Italy [6]. In general, it should be noted that despite certain differences in approaches to the diagnosis of ASD in different countries, there is a persistent trend towards an increase in the incidence of the disorder. Many ASD related gens and associated symptoms are under investigation [7, 8]. Distinct genes are involved in ASD symptoms such as social behaviour, vocalisation, synaptic interaction and transmission, memory and learning [9]. Children with autism often have comorbidities not typically associated with neuropsychiatric manifestations. These comorbid conditions are associated with the pleiotropic effect of these genes, which requires the involvement of many specialists to refine the diagnosis and determine treatment approaches. These conditions include short stature and other growth disorders, obesity and difficulties gaining weight [10]. Gene signalling pathway changes in ASD can lead to both functional and organic brain disorders. [11]. Based on the above, it is possible to assume the possibility of targeted ASD syndrome-associated modulation and diagnosis based on the regulation of the expressive activity of the involved gene signalling pathways. A preliminary analysis of current literature has identified the leading pathogenetic factors of ASD as starting points for targeted modulation and diagnosis.

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Integrative components of main signaling pathways involved in pathogenesis of ASD and their basic characteristics

Immune, viral and metabolic factors. Particular attention is paid to the consequences of intrauterine viral exposure on the central nervous system. These include Rubella, Cytomegalovirus (CMV), Herpes Simplex Virus (HSV), Varicella Zoster Virus (VZV), Influenza, Zika virus, and SARS-CoV-2. These viral infections are more commonly involved in postnatal emergence of ASD [12]. Children with autism often exhibit iron metabolism disorders, primarily characterized by low ferritin levels in 30-50% of patients. A strong link also exists between impaired iron metabolism and risk of depression. In addition, a correlation was identified between elevated levels of transferrin and ASD symptoms. This also involves hyperperoxidation and activation of the immune system [13-17].

Neurotransmitter systems

Serotonin. Serum serotonin concentration was found to be increased in 25% of children diagnosed with ASD. The experimental data indicate the presence of polymorphisms in the serotonin transporter gene (SERT) and associated impairments in social interaction, communication, and repetitive behaviour patterns [18].

Oxytocin. Oxytocin plays a leading role in regulating stress and social bonds. Correlations between social deficits and hypermethylation of the oxytocin receptor gene were identified in patients with ASD. Interactions between oxytocin and serotonin receptors, which are located mainly in closely related brain structures (e.g., the amygdalae and dorsal raphe nuclei), regulate social and emotional interactions. The ability of oxytocin to suppress serotonin signalling pathways has been demonstrated [19-21].

N-methyl-D-aspartate (NMDA) receptors. NMDA receptors are glutamate receptors that mediate excitatory neurotransmission and are a key factor in memory formation. In ASD patients with stereotyped behaviour the anti-NMDA antibodies has been detected. Evidence suggests that inhibition or excitation of NMDA receptors may influence ASD symptoms [22-24].

Synaptic proteins and structural regulation

SHANK proteins. The SHANK gene family encodes proteins crucial for the integrity and composition of excitatory glutamatergic synapses. The highest expression levels were detected in the striatum, prefrontal cortex, cerebellum and hippocampus. SHANK gene mutations can lead to NMDA receptor hypofunction and the manifestation of ASD symptoms [25-28].

Solute Carrier (SLC) family. The solute carrier (SLC) family plays a key role in transmembrane transport and secretion. Mutations in at least 71 of these genes are related to a spectrum of human neurological disorders. Neurological phenotypes linked with SLC mutations include epilepsy, intellectual delay, and autism. Polymorphisms in the serotonin transporter gene SLC6A4 are associated with behavioural instability in children with ASD [29-31].

Biomarkers and treatment considerations

Dysregulation in the aforementioned regulatory networks in ASD is related to prenatal viral exposure, metabolic and immune disorders, changes in neurotransmission and in structural synaptic protein, which may serve as a rationale for identifying potentially diagnostically significant biomarkers. Substantial attention is being paid to studying the diagnostic importance of biomarkers in ASD. It concerns protein and peptide-based biomarkers, metabolite- based and transcriptome based. Most biomarkers are still experimental, and challenges like cost, diversity, and ethical concerns remain [32, 33]. The aim of our semantic review was to identify, based on current research, potentially clinically significant biomarkers and opportunities for targeted therapy.

Fig. 1 shows how metabolic mechanisms and gene signalling pathways in ASD are linked to potential for biomarkers detection.

In accordance with the outlined pathogenesis, the subsequent review proceeded ton the details in each of the mechanisms involved.

Viruses and immune activation

The precise role of viruses in ASD symptom development beyond their specific pathogenetic mechanisms of CNS impairment remains, to a certain extent, unexplored.

Rubella virus. In congenital rubella syndrome, the risk of developing ASD and neurodevelopmental disorders is primarily associated with impaired retinoic acid metabolism and liver damage. This damage can be extensive, potentially with CNS and multiorgan involvement. There is a possibility of inhibition of the enzyme that converts retinol to retinoic acid, leading to retinoid accumulation and subsequent severe liver damage [34]. Furthermore, neuroimaging studies have revealed signs such as encephalomalacia, periventricular calcifications, and temporal lobe atrophy associated with gliosis and demyelination [35]. Autopsy results show the virus directly infected nerve cells in the cerebral cortex [36]. It is also important to note that retinoic

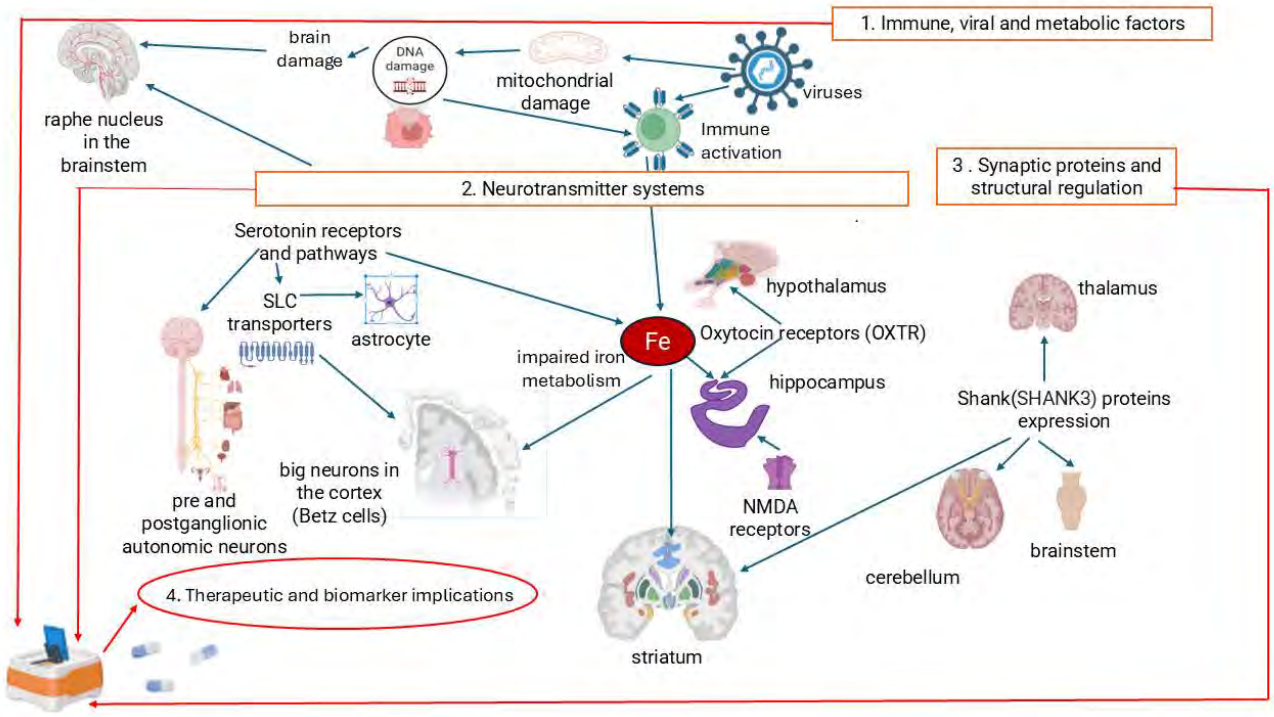

Figure 1. Integration of main signaling pathways involved in the pathogenesis of ASD and their sites in the brain.
1. Immune, viral and metabolic factors: during intrauterine development, viruses can damage brain mitochondrial DNA, with consequent immune potentiation and contributing to postnatal ASD signs Iron metabolism is commonly impaired in ASD. The location of transferrin receptors is the hippocampus, large cortical neurons, and striatum. 2. Neurotransmitter systems: serotonin levels are often elevated in ASD. Receptors and pathways are located in the raphe nucleus of brainstem, hippocampus, and pre-/postganglionic autonomic neurons. Oxytocin receptor (OXTR) hypermethylation in the amygdala and hypothalamus is observed in ASD. Mutations in SLC transporters (e.g., in SLC6A4) affecting nutrient, ion, drug, and neurotransmitter transport to neurons and astrocytes, as well as serotonin reuptake, are identified in ASD patients with emotional lability. Anti-NMDA antibodies found in ASD related stereotypical behaviours. Receptors are prevalent in hippocampal excitatory synapses. 3 Synaptic proteins and structural regulation: mutations in SHANK genes, highly expressed in the prefrontal cortex, brainstem, striatum, thalamus, cerebellum and hippocampus have been identified in ASD phenotypes and can lead to NMDA hypofunction. 4. Biomarker and therapeutic implications: The potential for the detection of diagnostic biomarkers could be realised through the integration of metabolic and gene signaling pathways.

acid plays a key role in differentiation and CNS regeneration and serves as a modulation factor in numerous signalling pathways and stimulates protein kinases during neurodevelopment and synapse formation [37].

The rubella virus can directly damage the CNS, resulting in progressive encephalitis characterised by white matter destruction, perivascular inflammation, and degenerative processes. Consequences include progressive dysarthria and ataxia due to cerebellar atrophy [38]. These manifestations are highly associated with ASD signs.

Cytomegalovirus. For cytomegalovirus (CMV) infection, an association has been revealed between prenatal detection of the virus and SRS (social responsiveness scale) scores in children of mothers diagnosed with ASD [39]. The study of 74,872 children, those diagnosed with autism (based on diagnosis codes), had a strong correlation with prior CMV infection (Hazard Ratio = 2.5) compared to the control group [40]. Cytopathologic assessment of foetuses infected with CMV has revealed necrosis, microglial nodules, microglial activation, astrocytosis, and vascular changes indicative of encephalitis [41]. Immunofluorescence and RNA-sequencing of CMV-infected cerebral organoids detected anomalous expression of genes in excitatory neurons, inhibitory neurons, and, more significantly, in intermediate progenitor cells. These alterations affected pathways involving DYRK kinases (dual-specificity tyrosine-regulated kinases that phosphorylate proteins, regulate proliferation, cell resistance and programmed cell death), SHH signalling (sonic hedgehog signalling pathway that regulates differentiation, morphogenesis and cell growth), neurodegeneration, axon guidance, Hippo signalling, and dopaminergic synapses. In CMV infection, there are 2,208 of 4,029 ASD related quantified genes upregulated, and only 236 are dysregulated [42].

Herpes simplex virus. Significantly higher levels of anti-HSV-2 antibodies were detected during mid-pregnancy in mothers of children with ASD compared with anti-Toxoplasma, anti-rubella and anti-HSV-1 antibodies [43]. Although this correlation was not con-

firmed in another study [44]. Nonetheless, HSV is a neurotropic virus capable of causing significant CNS damage. In a review by Duarte L.F. et al., it was also shown that HSV-1 replicates within neurons via a latent episome with minimal viral protein expression. Acute HSV-1 infection, however, can cause herpetic simplex encephalitis (HSE), characterised by apoptosis in affected cells. Autophagy acts protectively against HSV replication and is also a key regulator of neurogenesis, supporting stem cell pools enriched in areas like the sub-ventricular zone and hippocampus. HSV-1 infection can result in neuronal mitochondrial DNA (mtDNA) degradation. Furthermore, HSV-1 infection increases microglial reactive oxygen species (ROS) with consequent neuronal degeneration. Presumably, this occurs due to activation of ERK1/2 signalling pathways, Toll-like receptor 2 (TLR2) and p38 MAP kinase. The damage to DNA triggers HSV-1 replication in non-differentiated neuronal cells but is inhibited in mature neurons. This damage results in mutations of DNA and facilitates viral replication within undifferentiated neuronal cells and contributes to HSV-1 latency [45].

Influenza virus type A. This suggests that maternal influenza virus type A (IVA) infection during pregnancy can dysregulate cortical lamination and create an excitatory/inhibitory synapse imbalance during development, potentially leading to later neurodevelopmental disorders [46]. Another experimental study demonstrated that prenatal IVA exposure in mice induces ASD-analogous symptoms in male offspring, including decreased levels of oxytocin and serotonin, induced aggression and locomotor activity. This study also demonstrated changes in microglial density and increased levels of catecholamines in males [47]. Despite conflicting data that refute this association [48], there is a study in which influenza viruses were detected during pregnancy in 8% of mothers of children with ASD [49].

COVID-19 virus. The COVID-19 virus may play a specific role by changing concentrations of insulin-like growth factor (IGF-1). IGF-1 is a key factor for neurodevelopment, including myelination during pre- and postnatal periods, and is implicated in ASD. IGF-1 signalling (often involving translational regulation) is controlled via pathways like the IGF-1R/IRS1/PI3K/AKT/mTOR pathway, which regulates cell cycle, growth, proliferation, and differentiation [50]. Children with ASD carrying the rs12579108 polymorphism of the IGF-1 gene promoter and the AA genotype exhibited decreased IGF-1 levels [51]. The comparatively higher concentrations of IGF-1 within the cingulate gyrus of post-mortem brain tissues from ASD patients were demonstrated in a review by Jiamin S. et al. Low urinary IGF-1 levels, reflecting serum concentrations, were also noted. Furthermore, IGF-1 treatment has shown efficacy in improving ASD-like symptoms in various models and in related neurodevelopmental disorders [52]. The meta-analysis by Long J, Liao X, Han K, et al. revealed that diminished IGF-1 blood levels are related to the severity of ASD symptoms [33]. Table 1 illustrates the specific effects of prenatal viral exposure on ASD-related CNS damage, and Fig. 2 outlines the integration of the implicated genetic signalling pathways.

Iron metabolism and ferroptosis. Several studies suggest a role of ferroptosis in ASD pathogenesis. Involved in various iron-dependent conditions as well as in ASD, ferroptosis is a regulated, non-apoptotic cell death program characterised by iron - dependent peroxidation of lipids. In children with ASD, compared with the control group, increased expression of regulating ferroptosis genes was observed. In ASD, two ferroptosis-related molecular clusters were identified, exhibiting distinct immune heterogeneity. Cluster 2, characterised by a higher immune score and greater immune cell infiltration, showed a stronger immune response and significant enrichment in immune-related signalling pathways. Furthermore, a ferroptosis score model showed potential for predicting ASD subtypes and immune status. Higher ferroptosis scores were related to immune stimulation while decreased scores were linked to immune quiescence. This ferroptosis model could predict ASD subtypes and immune status. Genes found to be overexpressed in Cluster 1 included Fbxw7 (induces apoptosis and growth arrest and inhibits the epithelial-to-mesenchymal transition), ALB (main transporter of zinc in plasma, binds 80% of zinc, colloid and osmotic pressure regulation), MafG (associated with stimulated microgravity and radiation MC3T3-E1 apoptosis), AKR1C2 (activates PI3K/AKT signaling pathway, is the key factor of cell survival, cellular accrual and multiplication), RB1 (promoter of pR protein provides instructions for making a protein called pR that regulates uncontrolled cell growth) and ARNTL (blood pressure, body temperature and circadian rhythm regulation and associated with Th17-cell proinflammatory immunity at the mucosal level). There was also enhanced expression of CS (citrate synthases, which promotes the coupling of AcCoA with oxaloacetate (OAA) and TMBIM4 (transmembrane BAX inhibitor motif-containing protein 4, which helps regulate apoptosis and involved in promoting cell migration [53-55]. Ferroptosis is distinct from other regulated cell death (RCD) processes like pyroptosis, necrosis, autophagy and apoptosis. Mediated by Fe^{2+}-dependent lipid peroxidation, it has unique biological and pathophysiological characteristics [56, 57]. Ferritin metabolism pathways, including ferritin autophagy pathways involving ATG5-ATG7-NCOA4 and the p62-Keap1-NRF2 axis, are key modulators of intracellular Fe^{2+} levels and the synthesis of ROS. NCOA4 operates as a high affinity receptor for ferritinophagy (ferritin autophagy); its overexpression leads to ferritin degradation and promotes ferroptosis [58, 59].

Table 1. Impact of prenatal viral exposure on metabolism, CNS pathology, and ASD signs

Virus	Proposed mechanisms	CNS pathological findings	ASD-related associations	Evidence strength
Rubella	Altered retinoid metabolism; hepatic dysfunction; enzyme damage (retinol → retinoic acid conversion)	Encephalomalacia, periventricular calcifications, temporal lobe atrophy, gliosis, demyelination; direct cortical infection; progressive encephalitis with white matter destruction, perivascular inflammation, cerebellar atrophy	Signs consistent with ASD; neurodevelopmental impairment linked to retinoic acid dysregulation	weak
Cytomegalovirus	Aberrant gene expression in excitatory/inhibitory neurons and progenitor cells; dysregulation of DYRK kinases, SHH, pluripotency, Hippo- dopaminergic synapses	Necrosis, microglial nodules, astrocytosis, vascular changes (encephalitis)	Higher ASD risk (HR = 2.5); maternal infection linked to altered SRS scores; 236 ASD-related genes dysregulated	weak
Herpes simplex virus	Latent episome replication; apoptosis; autophagic regulation of neurogenesis; mitochondrial DNA degradation; ROS increase via TLR2/p38/ERK; MAPK/JNK activation; DNA damage response alteration	Herpetic encephalitis; neuronal apoptosis; mitochondrial dysfunction; neurodegeneration; DNA mutations in undifferentiated neuronal cells	Mixed evidence: some studies show maternal HSV-2 antibody association with ASD, others do not; mechanistic plausibility via neurodegeneration	weak
Influenza Virus A	Downregulation of Apc2 (cortical lamination), Mdga1 (neuronal migration), and neurogenesis/migration genes; excitatory/inhibitory synapse imbalance	Altered microglia density; catecholamine changes; reduced oxytocin/serotonin; altered behavior in experimental models	ASD symptoms in mice (aggression, hyperactivity); human study: ~8% autism incidence in exposed offspring (contradictory data also reported)	weak
COVID-19	Reduced IGF-1 levels; IGF-1R/IRS1/PI3K/AKT/mTOR pathway dysregulation; IGF-1 promoter polymorphism (AA genotype)	Altered myelination; neurodevelopmental impairment; elevated IGF-1 in cingulate gyrus (postmortem); decreased urinary IGF-1	Lower serum IGF-1 linked to ASD; IGF-1 treatment improves ASD-like symptoms in models	moderate

Furthermore, significantly lower ferritin levels were identified in children with severe symptoms of ASD compared with the control group [56]. Similarly, compared with the control group, single nucleotide polymorphisms (SNPs) were identified in the transferrin receptor gene (TFRC) and the ferroportin gene (SLC40A1) in children with severe symptoms of ASD, which may be considered a potential biomarker of this condition [60]. In ASD, serum concentrations of ferritin have been negatively correlated with parasomnias [61] and positively correlated with restless legs syndrome [62]. In children with ASD and anaemia, 28.07% had low haemoglobin and ferritin levels [63]. Ferritin levels in pregnancy were negatively correlated to offspring DNA methylation levels at specific loci postnatally [64]. Children with ASD have been found to have reduced levels of ceruloplasmin and transferrin, and increased lipid peroxidation levels, compared with their healthy siblings, which was directly associated with regression of language skills [65]. Transferrin mRNA expression was observed in the plexus chorioideus (oligodendrocytes) as well as in cortical, hippocampal, medullary and basal ganglianeurons. In contrast, hippocampal expression is notably low, potentially increasing this region's vulnerability to iron-induced oxidative stress [66]. In a mouse model exhibiting extensive amyloid pathology, cognitive impairment, neuroinflammation, and deficits in synaptic potentiation/transmission,

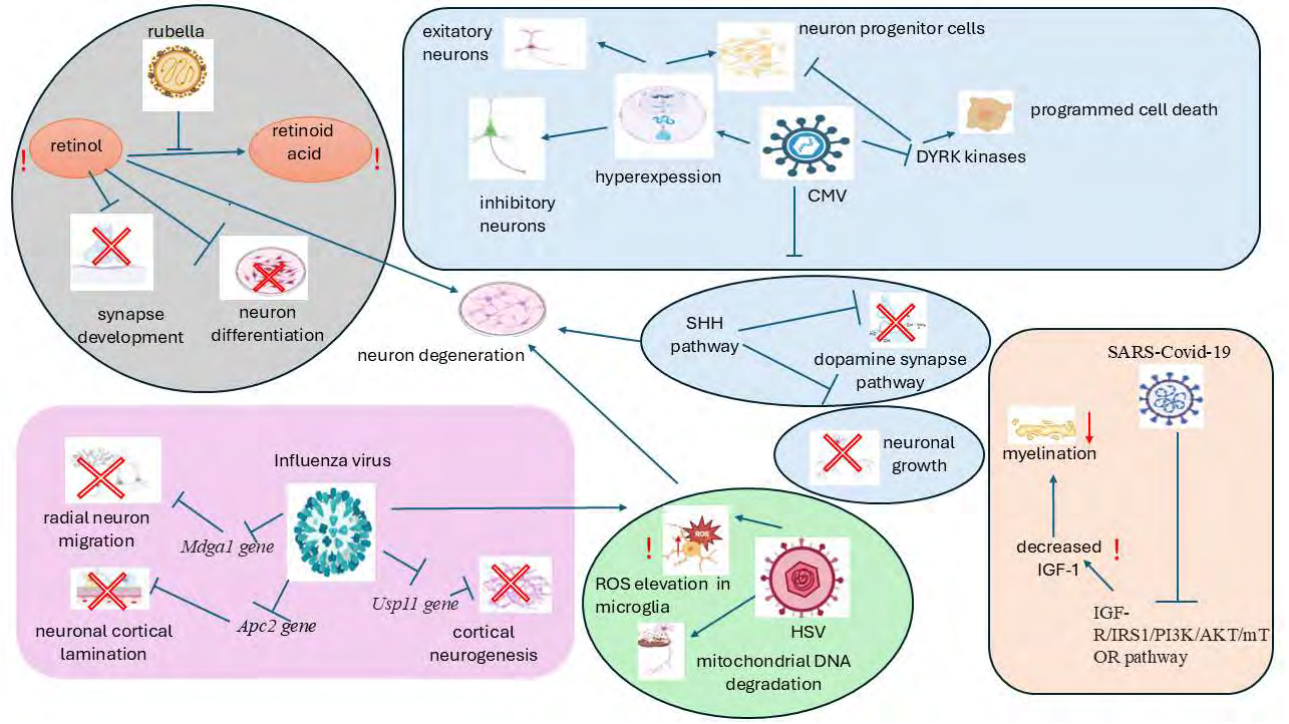

Figure 2. Cohesive effects of prenatal viral exposure on gene signalling pathways in potential ASD pathogenesis.
Rubella: Inhibits retinol-to-retinoic acid conversion → Retinol accumulation → Impaired synapse development, blocked neuronal differentiation, potentiated neurodegeneration. CMV: results in gene hyperexpression in effector and suppressor neurons and in neuron progenitor cells (NPCs). Concurrently, CMV has been shown to inhibit DYRK kinases, thus potentiating programmed cell death and inhibiting NPCs. The inhibition of the SHH pathway by CMV suppresses neuronal growth and alters dopamine synapse pathways, leading to neurodegeneration. HSV induces the production of ROS in microglia and DNA degradation in neurons, as a result neuronal degeneration also occurs. The influenza virus A (IVA) inhibits Apc2, Mdga1, and Usp11 gene expression. These genes are the key factors for neuronal cortical lamination, radial neuron migration, and cortical neurogenesis, respectively. IVA infection also results in altered microglia density. COVID-19 decreases IGF-1 levels (regulated by IGF-1R/PI3K/AKT/mTOR pathway) leading to impaired myelination. The integral effects of viral exposure result in degeneration of neurons. "!" indicates potential biomarkers.

the increased transferrin receptor (TfR1) expression in cortical tissue was linked to HIF-1α transcriptional activation (hypoxia-inducible factor 1-alpha, an oxygen-dependent transcriptional activator regulating hypoxia adaptation genes) [67]. Transferrin (Tf) reduces cellular demise and potentiates differentiation of neurons, accompanied by enhanced IL-10 production, making it a promising candidate for regenerative strategies in neurodegenerative diseases [68]. Microglia in the brain preferentially acquire iron either from transferrin (Tf) or non-Tf sources relative to the state of polarisation. The uptake of non-transferrin-bound iron is enhanced during proinflammatory responses, under which conditions microglia also sequester both extra- and intracellular iron [69]. Depending on the level of iron in the brain, a variably low concentration of transferrin is observed in the cerebrospinal fluid, underlying the pathophysiology of neurodegenerative proteinopathies [70]. Therefore, in children with autism, the ferroptosis may be linked to the severity of neurodegenerative processes potentially triggered by immune activation against immature neurons in specific areas of the brain. Ultimately, this may lead to a reduction in transferrin and ferritin levels, as shown in Fig. 3. It should also be noted that the clinical significance of ferritin and transferrin levels as diagnostic biomarkers for ASD remains unclear and requires further investigation [14, 71, 72].

Neurotransmitter systems

The role of serotonin in ASD. Serotonin is a neurotransmitter composed of 14 different molecular subtypes, which facilitates its interaction with a broad spectrum of receptors implicated in memory and cognitive function. Serotonin, a monoamine neurotransmitter that functions within the central nervous system (CNS), is implicated in a multitude of processes, including cognition and memory. Serotonin levels are significantly reduced under the influence of stress, thereby modulating the immune response, which leads

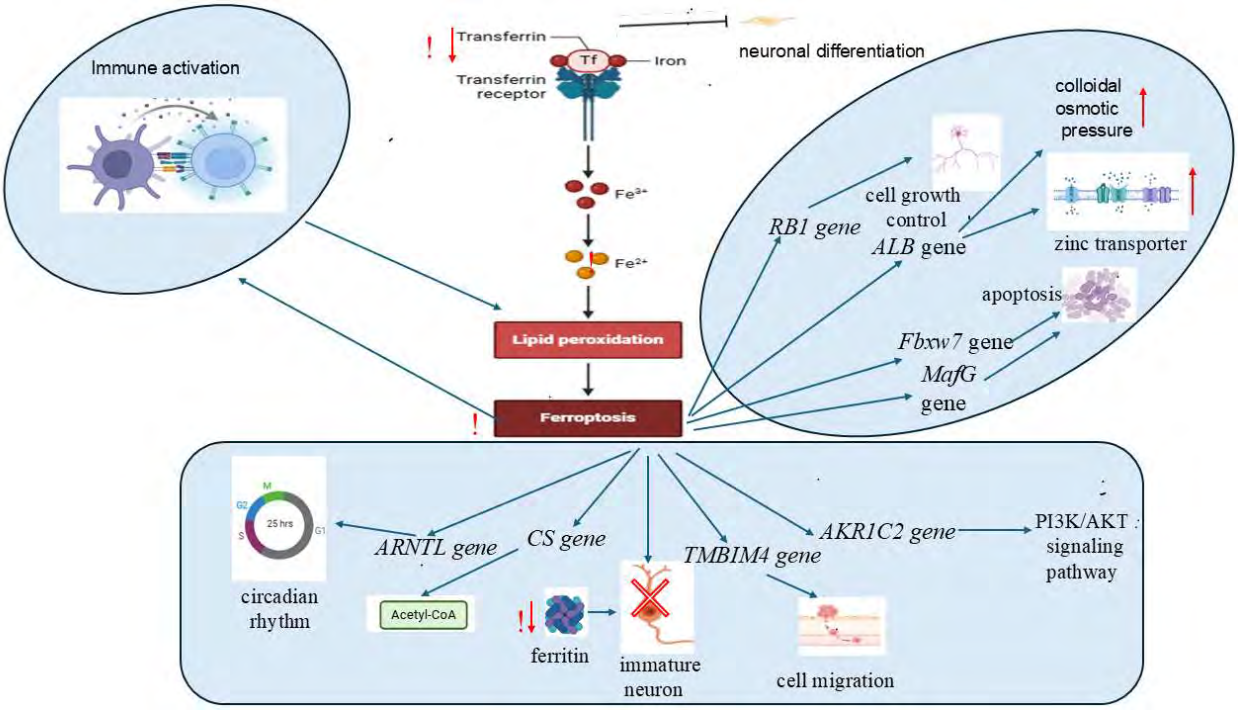

Figure 3. Potential role of dysregulated ferroptosis and iron metabolism in ASD-associated signs.
It is thought that neuronal immaturity in ASD acts as a trigger for immune activation and subsequent intracellular lipid peroxidation. Ferroptosis also instigates Fe^{2+}-dependent lipid peroxidation and activates the ferritin autophagy pathways. This results in ferritinophagy and a decrease in ferritin concentrations. At the same time, it has been shown that ferroptosis enhances the expression of Fbxw7, MafG, and AKR1C (involved in cellular signaling and oxidative stress response), with consequent activating of the PI3K/AKT signaling pathway (key in cell survival and growth), as well as RB1 (regulation of cell cycle), TMBIM4 (cell death modulation), ALB (colloid oncotic pressure), CS (citric acid cycle enzyme), and ARNTL (circadian regulation). This, in turn, leads to the activation of multiple molecular mechanisms like cell growth and migration, as well as apoptosis, colloid oncotic pressure, zinc transmembrane transport, citric acid cycle, circadian regulation and Th-17 cell activation with mucosal proinflammatory response. Simultaneously, active ferroptosis could reduce transferrin levels, thereby impairing neuronal differentiation. "!" indicates potential biomarkers.

to the suppression of pro-inflammatory cytokine production, in particular tumour necrosis factor (TNF-α). Serotonin 5-HT1A and 5-HT2A receptor dysregulation may affect apoptosis in inflammatory cells, potentially making these receptors valuable therapeutic targets. Hyperserotoninaemia has been observed in 25% of children with ASD and has become the first identified biomarker for this condition. Damage to serotonin signalling pathways in ASD has been observed in the brain both post-mortem and in ante-mortem neuroimaging studies. Genetic linkage and association studies examining both whole blood serotonin levels and ASD risk point to a chromosomal region containing the SERT gene, particularly in males. Rare variants of polymorphisms in the serotonin transporter (SERT) gene have been identified in families with ASD, and increased serotonin reuptake has been observed in cellular models. The SERT Gly56Ala variant in knockout mice led to increased serotonin clearance, elevated blood serotonin levels, increased receptor sensitivity, as well as impairments in communication, social interaction and repetitive movements. The 5HT2A receptor is predominantly located in glutamate neurons within the hippocampus, in the frontal and parietal cortices, as well as in the midbrain dopaminergic neurons and in endocrine cells of the anterior pituitary. Serotonin 5-HT2A receptor stimulation elicits various effects, including stimulating glutamatergic neurons in the frontal/parietal cortex, inhibiting dopamine release, and augmenting thesecretion of neurohypophysis peptide hormones (e.g., growth hormone, luteinizing hormone, adrenocorticotropic hormone, prolactin). These 5HT2 receptors are in different regions of the brain and are responsible for different functions. In a mouse model of autism, administration of a 5-HT2A receptor antagonist into the dorsomedial striatum reduced excessive grooming behaviour and reversed learning deficits [73]. Hypomethylation of the human serotonin receptor 4 (HTR4) promoter has been identified as a significant marker for male ASD [74]. Evidence has demonstrated that the serotonin 1A receptor, which is expressed in the striatum, has the capacity to regulate social behaviour in individuals diagnosed with ASD [75, 76].

Serotonin regulation (SLCsproteins)

The solute carrier transporters (SLCs) represent a large superfamily of over 450 proteins, which exhibit a range of functions, structures, and expression patterns. These proteins help remove neurotransmitters (e.g., dopamine, norepinephrine, serotonin) from the synaptic cleft or target compartment and play an essential role in blood-brain barrier function [77]. Abnormalities in genes encoding SLC transporters can lead to various neurological diseases. SLC6A4, the gene responsible for coding the serotonin transporter (SERT), is pivotal in regulating serotonin, a neurotransmitter that plays a fundamental role in regulating emotion, mood, and social behaviour. SLC6A4 gene variants can impact transporter protein structure and function and are linked to ASD [78]. SLC4 genes participate in neuronal modulation, brain function maintenance, cellular growth, and activation of the PI3K/AKT/mTOR signalling pathway. Dysfunctional SLC proteins can lead to intracellular acidosis and diminished nerve excitability. Associated alterations may include changes in exploratory or emotional behaviours, deficits in visual and auditory processing, altered sensory perception, and reduced locomotor activity [79].

In ASD, dysregulation of serotonin levels impairs brain development and is associated with anxiety, depression, and stereotyped behaviours. Self-injurious behaviour has further been connected to serotonin transporter gene polymorphisms [80]. According to the systematic review conducted by Esposito D., Cruciani G., Zaccaro L., et al., hyperserotonaemia was found to be closely related to intellectual disability in ASD and inversely associated with verbal IQ and memory performance [81].

The role of tryptophan

Tryptophan (TRP), the precursor of 5-HT, shows altered metabolism in ASD. In children with ASD, significantly decreased expression of TRP metabolic pathway genes has been demonstrated. These include MAOA (monoamine oxidase A, which breaks down serotonin, epinephrine, norepinephrine, and dopamine), HAAO (3-hydroxyanthranilate 3,4-dioxygenase, a cytosolic enzyme in glial cells that catalyses quinolinic acid synthesis), and AADA (aminoadipate aminotransferase, a precursor of kynurenic acid with neuroprotective properties) [82]. A study of 65 children diagnosed with ASD revealed elevated serum Brain-Derived Neurotrophic Factor (BDNF) concentrations. At the same time, TRP and kynurenic acid levels were diminished compared to a matched control group [83]. A review by Santana-Coelho D. highlights the significance of the kynurenine pathway as a primary metabolic route for TRP. This pathway metabolizes tryptophan and generates several neuroactive metabolites with neuromodulatory effects via actions on glutamatergic and cholinergic receptors. It has also been identified as a potential therapeutic target for inflammatory disorders, including those potentially triggered by maternal immune activation during pregnancy [84].

Therefore, the dysregulation of serotonin pathways and variations in blood serotonin levels observed in individuals with ASD appear closely related to SERT gene variations, immune activation, and consequently impaired tryptophan metabolism. This is summarised in Fig. 4.

Oxytocin pathways

Oxytocin (OT), a neuropeptide, has been demonstrated to be involved in both social and reproductive behaviour in animals and humans. In the context of human social behaviour, three oxytocin signalling genes have received frequent attention: OXT (the structural gene for oxytocin), OXTR (the oxytocin receptor), and CD38 (the oxytocin secretion gene). The expression of the three genes selected from the oxytocin pathway was found to be enriched in subcortical and olfactory regions. Furthermore, high co-expression with multiple dopaminergic and muscarinic acetylcholine pathway genes was observed, indicating an anatomical basis for interactions between these critical pathways. The distribution of oxytocin pathway gene expression corresponds with brain regions involved in processing anticipatory, appetitive, and aversive cognitive states.

The oxytocin signalling system interacts with dopaminergic and muscarinic acetylcholine signalling, thereby modulating cognitive processes involved in complex human behaviours [85]. Genes supporting the OT system are overexpressed in specific cortical regions (notably the precentral gyrus) but underexpressed in certain subcortical and central structures, including the basal ganglia, limbic system, and brainstem [86]. OT and OXTR in the brain regulate neuronal excitability, network oscillations, synaptic plasticity, and social recognition memory [87]. OXTR gene polymorphisms (rs2254298, rs53576) play an essential role in ASD development [88].

Individuals with ASD show higher OXTR binding in the nucleus basalis of Meinert (involved in visual attention) but significantly lower OXTR binding in the ventral pallidum (part of the mesolimbic reward pathway involved in motivated behaviours). Notably, in patients diagnosed in early childhood, no binding was found in the ventral pallidum [89]. Oxytocin receptor (OXTR) gene hypermethylationhas been found in individuals with ASD and correlates directly withsocial responsibility deficits. This hypermethylation also correlates with clinical symptoms and hypoconnectivity between cortico-cortical areas involved in theory of the mind.

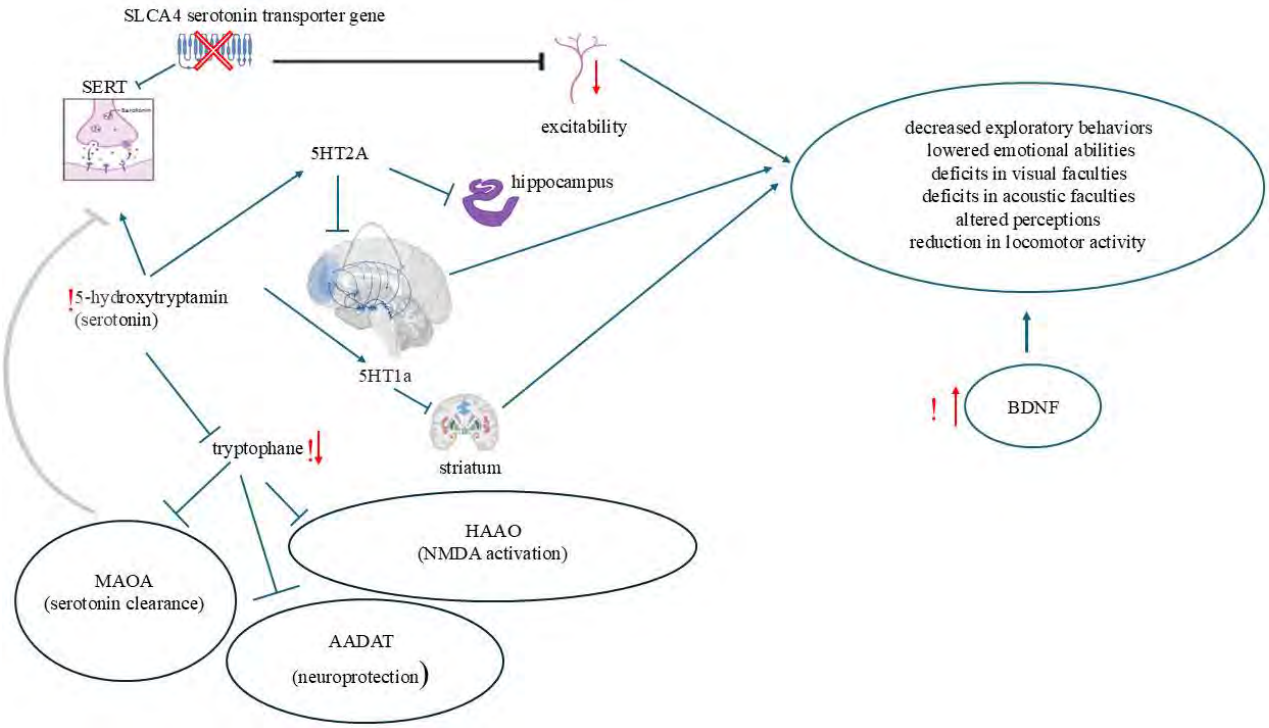

Figure 4. Dysregulation of serotonin pathways in ASD.
In ASD, the variations in the serotonin transporter gene (SLC6A4) have been demonstrated to result in impaired neuronal metabolism, decreased excitability and reduced brain serotonin clearance. Consequently, the changes in serotonin level can give rise to a state of dysregulation of 5HT2A receptors, located in the frontal and parietal cortices, in relation to inhibition of dopamine and neurohypophysis hormones secretion in the hippocampus, and inhibition of 5HT1A receptors located in the striatum. A decrease in tryptophan levels, a precursor of serotonin, has been demonstrated to result in diminished expression of genes within the tryptophan pathway. This phenomenon has been shown to exert an influence on the enzymes involved in serotonin clearance, neuroprotection, and N-methyl-D-aspartate (NMDA) receptor activation. The observed changes are concomitant with the elevation of serum BDNF levels. The following provides a synopsis of signs that are associated with ASD. Impaired SERT activation could trigger a cascade of serotonin pathway dysregulation, causing a vicious circle and the progression of ASD symptoms. "!" indicates potential biomarkers.

Furthermore, methylation at a specific CpG site in exon 1 relates positively to social responsiveness deficits and hyperconnectivity between striatal and cortical brain areas in ASD [90]. Significantly increased serotonin and decreased OT levels have been identified in the blood of children with ASD [91]. A meta-analysis of a total of 31 studies, incorporating a sample of 1231 individuals diagnosed with ASD, has revealed a decrease in OT levels. The analysis also reveals a more significant decrease in oxytocin levels in children [92]. The interaction between serotonin and oxytocin plays an essential role in social behaviour. Oxytocin induces serotonin release, subsequently influencing the 5-HT1A receptor system by regulating its availability in key brain regions involved in social behaviour, such as the amygdala and insula [93]. Presynaptic OT receptors on dorsal raphe projections to the nucleus accumbens induce 5-HT release; furthermore, activation of postsynaptic 5-HT1B receptors is required for establishing social preference [94].

Reduced function or interaction ("blunting") of OXTR within 5-HT2AR and especially 5-HT2CR heteroreceptor complexes may contribute to depression and other psychiatric disorders involving social behaviour disturbances [95]. Rats administered the 5-HT agonist 5-methoxytryptamine, inducing hyperserotonemia, exhibit decreased OT in the hypothalamic paraventricular nucleus and display "autism-like" behaviours [96]. These findings suggest the existence of mutual interactions between the 5-HT and OXT systems. Evidence from 12 randomised controlled trials including 498 ASD patients highlights thata high daily dose of 48 IU intranasal oxytocin significantly alleviated social impairments but had a limited impact on repetitive behaviours [97]. Another meta-analysis showed intranasal oxytocin enhanced social and communicative abilities in ASD patients [98]. Intranasal oxytocin administration appears moreeffective when combined with behavioural therapy; however, the magnitude of its effects varies, and long-term outcomes require further investigation [99].

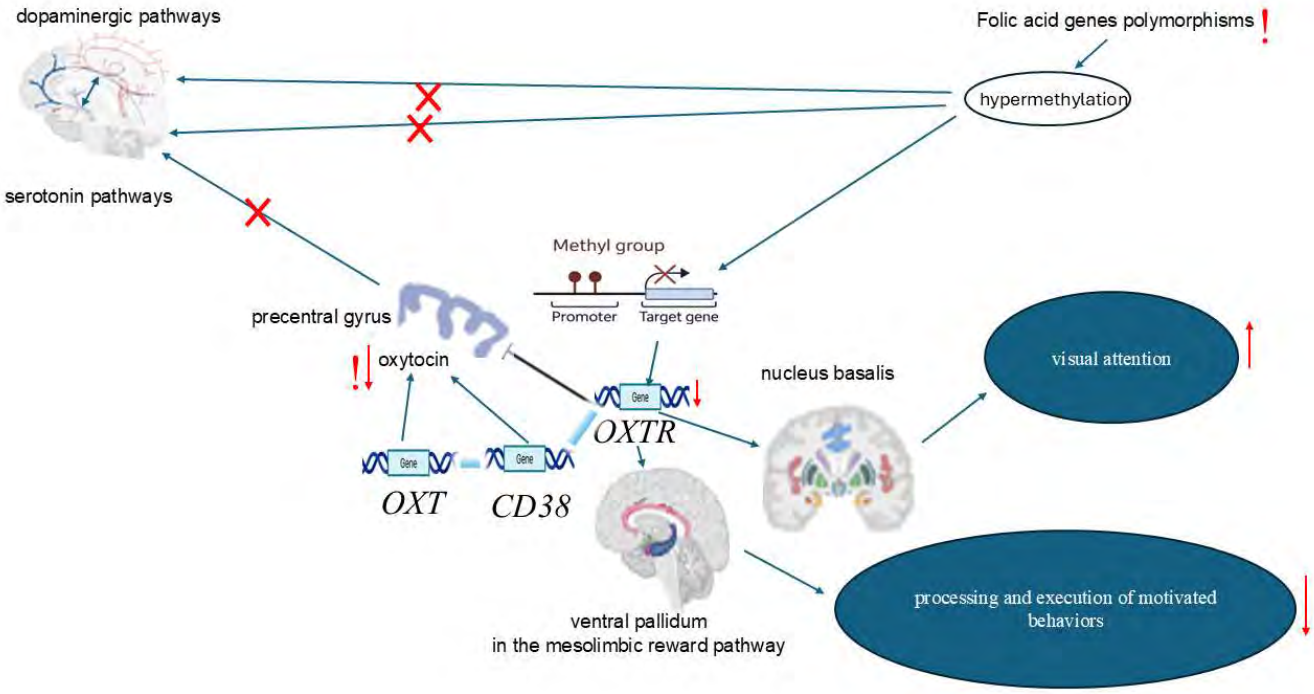

Figure 5. Oxytocin pathways alteration in ASD.
The hypothesis suggests that folic acid cycle gene mutations may result in impaired methylation and alterations to the OXTR-oxytocin pathway, as well as folate deficiency affects serotonin and dopamine production . Methylation of the OXTR resulted in decreased expression and heightened binding levels of the OXTR in the nucleus basalis with diminished expression levels in the ventral pallidum. Diminished serotonin has the potential to modify the expression of both serotonin and dopamine, thereby inducing. This could result in induced disorganisation within the domains of visual attention and motivated behaviours processing, a phenomenon that has been observed in individuals diagnosed with ASD. "!" indicates potential biomarkers.

Therefore, alterations in oxytocin signalling pathways, influenced by close co-expression and interactions with serotonin and dopamine systems, likely play a key role in the cognitive and social manifestations of autism. This is summarised in Fig. 5

Synaptic proteins

Glutamate receptors. Glutamate receptors are major mediators of excitatory neurotransmission at synapses in the central nervous system. The two major subtypes of glutamate receptors that cluster on the postsynaptic membrane are N-methyl-d-aspartate (NMDA) and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptors. The NMDA subtype of glutamate receptor (NMDAR) is critical for synapse development, neuroplasticity, and pathological neurotoxicity; its synaptic levels critically regulate brain function. N-methyl-d-aspartate receptors (NMDARs) are a distinct type of ligand-dependent ionotropic receptor that possess a unique combination of biophysical and functional characteristics. These receptors play a crucial role in the cellular mechanisms of new neuronal network formation and the strengthening of synapses. This role is critical to the development and maintenance of cognitive processes that are vital to higher cognitive functions in humans [90, 91]. NMDARs exhibit high calcium permeability and require binding of both glutamate and an allosteric co-agonist (glycine or D-serine for channel opening. Excessive concentrations of excitatory amino acid neurotransmitters can lead to glutamate receptor overexcitation. The NMDA receptor is a complex supramolecular entity with several regulatory sites: the agonist binding site (L-glutamate), the co-agonist binding site (glycine/D-serine), and allosteric modulatory sites both on the membrane and within the ion channel (e.g., binding sites for divalent cations like Mg^{2+} and non-competitive antagonists like phencyclidine [100, 101].

Overexcitation of NMDA result in increased Ca^{2+} influx into neurons and a rapid increase in intracellular calcium concentration [102-104]. Disrupted NMDAR function is associated with various psychiatric disorders, including ASD. Multiple genetic variants in the NMDAR gene family (GRIN) have been found in individuals with ASD [105]. ASD-associated mutations and rare variants have been found in all NMDAR subunit genes: GRIN1 (encoding GluN1), GRIN2A (GluN2A), GRIN2B (GluN2B), GRIN2C (GluN2C), and GRIN2D (GluN2D). Among these, GRIN2B is currently considered the most predominant ASD risk gene [106, 107]. ASD is associated with changes in glutamate concentra-

tion, receptor desensitization, channel function (channelopathies), ion transport, receptor trafficking, surface expression, dendritic growth, spine density, and synaptic transmission [108]. Mice with the GluN2B-C456Y mutation exhibited decreased GluN2B and GluN1 protein expression and impaired NMDAR currents at GluN2B-containing Schaffer collateral-CA1 (SC-CA1) hippocampal synapses. Heterozygous Grin2b+/C456Y mice exhibited hypoactivity, anxiolytic-like behaviour, and moderately increased self-grooming in adulthood, although social interaction and communication appeared normal [109-112]. Mounting evidence suggests that impaired NMDAR signaling is a significant molecular mechanism underlying the pathogenesis of idiopathic autism.

Structural regulation

SHANK genes. Many ASD risk genes encode proteins involved in synaptic structural and functional integrity; notably, the SHANK gene family encodes major scaffolding proteins at the postsynaptic density. All three SHANK genes (SHANK1, SHANK2, SHANK3) have been implicated in ASD, but mutations in SHANK3 are often associated with more severe behavioural deficits. The SHANK3 protein acts as a scaffold supporting synaptic connections, ensuring proper signal transmission between neurons.

In this way, it ensures that the signals sent by one neuron are received by another. Animal models with ASD-associated Shank mutations exhibit relevant behavioural phenotypes, including impaired sociability, communication deficits, repetitive behaviours, and anxiety [113, 114]. Animal models carrying human autism-associated mutations also show NMDAR dysfunction. For example, mice with a transcriptional stop cassette inserted upstream of Shank3 exon 13 (encoding the PDZ domain) (Shank3+/ΔE13 and Shank3ΔE13/ΔE13) exhibit impaired hippocampal long-term potentiation (LTP) and a reduced NMDA/AMPA ratio at corticostriatal synapses [115, 116]. Other postsynaptic adhesion molecules, such as the neuroligin family, also play pivotal roles in ASD.

Neuroligins. The neuroligin expression exhibits significant heterogeneity among distinct neuronal types, manifesting in an isoform-specific manner. However, neuroglins 1, 2 and 3 are expressed in different synapses: neuroglins 1 in excitatory synapses, neuroglins 2 in inhibitory synapses, whilst neuroglins 3 are found in both types of synapses. Neuroligins interact transsynaptically with neurexins, cooperatively modulating synapse formation, specification, and NMDAR regulation. Genetic alterations in the NLGN1 gene are linked with ASD. Nlgn1 knockout mice (Nlgn1-/-) exhibit increased repetitive grooming and impaired spatial memory [117, 118].

Contactin-associated proteins (CNTNAP). CNTNAP2 is another high-risk ASD gene; it plays a role in synaptic cell adhesion and encodes contactin-associated proteins CNTNAP2 or CASPR2. CNTNAP2, a type I transmembrane protein highly homologous to neurexins, interacts with CNTN2 (postsynaptic protein of cell adhesion, contactin-2), which plays a crucial role in K^+ channel trafficking to myelinated axons in juxtaparanodal regions and the transport of GluA1 AMPAR subunits to dendritic spines [119-121].

Therefore, dysregulation or structural anomalies of scaffolding proteins like SHANK and synaptic adhesion molecules (e.g., neuroligins, CNTNAP2), may contribute to ASD phenotypes by affecting postsynaptic NMDAR activity and related signaling.

Discussion: clinical comparisons, suggested biomarkers, and modulation. It is becoming apparent that intrauterine CNS injury and maternal immune activation are the key factors in postnatal ASD phenotypes. Twin and sibling studies agree that autism has a broad genetic basis; there is also evidence of gene-environment interaction. The review focused on several key pathogenetic factors that remain to be fully clarified. These factors enable feasible diagnostic strategies and provide key insights into the integrated regulation of signalling pathways. Evidence indicates that intrauterine viral infections and lesions of structures (e.g. impaired synapse development and transmission) are contingent upon the virus type. Intrauterine viral infections distinctively affect diverse neuronal components and pathways. Intrauterine rubella infection can inhibit retinoid conversion to retinoic acid (RA), leading to CNS retinoid deposition. In physiological conditions RA mediates the growth of dendritic cells and stem cell differentiation with functional maturation of neurons. RA induces activity of BDNF and NGF (nerve growth factor, which is involved in cell differentiation) [122, 123]. RA insufficiency impairs synapse development and neuronal differentiation. Therefore, evaluating retinoid status could reflect the neuronal maturity and potentially serve as a biomarker for ASD caused by intrauterine rubella infection. In this regard, using retinoic acid preparations (e.g., all-trans retinoic acid, ATRA) might be promising for ASD patients with confirmed prenatal rubella exposure. ATRA has shown differentiation-inducing effects and therapeutic results in some blood cancers [124, 125].

HSV leads to more enhanced CNS immune activation resulting in encephalitis, cell apoptosis, neuronal mitochondrial DNA degradation and ROS elevation in microglia, leading to neurodegeneration. In this context, oxidative stress indicators and markers of neuroinflammation could be utilized. CMV infection can have a detrimental effect on cerebral organoids, with consequent activation of certain ASD-related pathways. Activation of these pathways ultimately leads toneuro-

degeneration and impaired dopamine signaling. Neuroinflammatory markers and those linked to dopamine signaling could serve as useful indicators.

Influenza virus primarily inhibits gene pathways related to neuron migration, cortical lamination and neurogenesis, and, while also alters microglia density and catecholamine levels. These effects could result in ASD-like phenotypes, potentially accompanied by reduced oxytocin and serotonin levels, thus informing biomarker selection and modulation strategies.

COVID-19 virus inhibits specifically the IGF-1, thus precipitating in dysregulation of myelinisation and differentiation of neurons. Elevated levels are also observed in major depressive disorders [126, 127]. In this connection, the IGF-1 neurotrophic effects could be dependent on the state of neurodegeneration and the activation of neuronal networks. This may indicate a discrepancy in the neurotrophic regulation of IGF1, depending on the prevalence of degenerative processes or neuronal network activation. In this regard, IGF1 could potentially serve as a promising marker of neurodegenerative state in ASD.

The data presented indicate that iron metabolism plays a significant role in the pathogenesis of pathological changes in ASD. Low concentration of transferrin and ferritin in patients with ASD is associated with processes of ferroptosis and ferritinophagy. The overexpression of brain cortical TfR1 increases apoptosis and promotes neuronal differentiation and antihypoxic adaptational reactions. Ferritin concentrations decreased in children diagnosed with ASD, with such declining being associated with ferroptosis and hyperperoxidation, a state of hypermethylation, the presence of parasomnias and restless legs syndrome. Diminished Tf levels also correlate with the loss of acquired language skills. In turn, ferroptosis and peroxidation related to immune and apoptosis pathway activation as well as to cell growth control, colloidal osmotic pressure, cell migration, and circadian rhythm. At the same time, dopamine was shown to stimulate iron uptake by macrophages, thereby promoting intracellular oxidative stress responses [128]. Moreover, the expression of dopamine receptors (D2) on blood lymphocytes is linked to the degree of subcortical cognitive deficit, suggesting a potentially important aspect of pathogenesis in this disorder [129]. Thus, immune activation with consequent ferroptosis could theoretically result in dopamine- associated symptoms in ASD. Therefore, the detection of serum transferrin and ferritin levels, in conjunction with immune markers of inflammation and oxidative stress, may offer a means of gauging the acuity of the neurodegenerative process, as well as the level of dopamine system a cognitive impairment involvement in manifestation of ASD.

With respect to the aforementioned, the identification of biomarkers indicative of immune activation and neuroinflammation in ASD has the potential to yield significant findings. It is evident that immune biomarkers are absent in 13% of patients with ASD, It is evident that immune biomarkers are absent in 13% of patients with ASD, which might indicate the presence of heterogeneous pathogenetic groups [130]. In such patients, the symptoms may be secondary and associated with genetic CNS disorders. The review by Stancioiu F., Bogdan R. and Dumitrescu R. [131] cites several meta-analyses that have demonstrated a lack of reproducibility and reduced sensitivity of biochemical, genetic and neuroimaging markers for ASD. Alongside this, inflammatory and immune biomarkers identified 87% of ASD cases. The increased serum neuron-specific enolase (NSE) concentration in 97.5% of ASD patients was observed, suggesting neuronal post-apoptotic release and considering this biomarker as indicative of neuronal damage severity in ASD.

Heat shock proteins (HSPs) are present in all human cells and are vital for the maintenance of normal protein synthesis and function. Elevated levels of antibodies against the HSP90 protein are detected in autoimmune processes associated with non-psychiatric conditions. Elevated levels of HSP90, depending on disease activity, have also been observed in patients with psychiatric symptoms associated with lupus, as well as in those with schizophrenia and compulsive symptoms of ASD [122, 123]. HSP70 has the capacity to bind to misfolded proteins, thereby assisting them in adopting their native conformation. Therefore, the increase in HSP proteins following cellular damage may serve as a protective mechanism for cell survival. HSP70 is detected in the extracellular space as a marker of cell death, subsequently interacting with TLR2 and TLR4 receptors on macrophages, dendritic cells and glial cells. Increasing HP70 levels slows down oxidative stress at the cytosolic and mitochondrial levels [132]. It has been shown that HSP72 is a highly sensitive marker of neuronal damage. A substantial increase in HSP70 levels has been observed in patients diagnosed with ASD in comparison to those diagnosed with ADHD [133]. HSP70 pharmacological modulation improves synaptic function and connectivity in ASD. HSP70 regulates neuronal activity and Nrf2 expression (nuclear respiratory factor 2), which is reduced in ASD. Sulforaphane (SF) extracted from broccoli, an isothiocyanate, activates HSP70, which in turn triggers the Nrf2 pathway, thereby promoting cell protection, potentially exerting a positive effect on ASD Sulforaphane (1-isothiocyanato-4-methylsulfiny-lbutane) is an antioxidant studied for its potential in ASD and other conditions, showing beneficial effects [134, 135].

Lipid peroxidation and mitochondrial dysfunction are the key pathogenetic factors of apoptosis and ferroptosis. This review supports the notion that these factors directly influence the intrauterine effects of CMV and HSV on the CNS (Fig. 2) and collectively modulated iron metabolism (Fig. 3). In patients with ASD, the

biochemical markers of mitochondrial dysfunction are elevated, including significant increase (all $p < 0.01$) in alanine, pyruvate, creatine kinase and lactate. Symptoms such as speech delay, impaired social interaction, cognition, motor function, repetitive behaviours and gastrointestinal symptoms have been associated with lactate, pyruvate, lactate/pyruvate ratio, carnitine and acyl-carnitines. Treatment targeting mitochondria, particularly carnitine and ubiquinol, seems to be helpful in ASD. Further studies could elucidate the role of mitochondrial dysfunction in ASD by better defining subgroups and understanding the mitochondrial changes seen in people with autism [136]. Thus, based on connections between immune activation, ferroptosis, peroxidation levels and neuronal mitochondrial dysfunction, further investigations into the detection of these biomarkers could be promising for diagnosis and treatment strategies. In ASD, an increase in ROS levels, along with overexpression of T-cells TLR-4 and NOX-2 was observed compared to controls [137, 138].

In ASD, the antioxidants such as N-acetylcysteine (NAC), have shown improvements in irritability as well as behavioural and communication symptoms, compared to placebo. NAC has been shown to reduce hyperactivity and irritability in ASD. Treatment with NAC and antioxidants had a good tendency towards improvement of irritability and hyperactivity symptoms [139]. A double-blind, placebo-controlled study was conducted to evaluate the safety and efficacy of glutathione alone and treatment with glutathione, vitamin C and NAC in children diagnosed with autism. Compared to placebo therapy, improvements in developmental skills and behaviour were observed with both glutathione and the combination therapy of glutathione, vitamin C and NAC in children with ASD [140, 141]. These data confirm that NAC, alongside the detection of ferroptosis and oxidative stress markers, could be a viable addition for ASD treatment strategies.

Serotonin plays an essential role in neurodevelopment, cognition and memory. SLC6A4 gene mutations affect the SERT leading to improper receptor positioning, which results in hyperserotoninemia, reduction of the TRP serotonin precursor tryptophan (TPR) and downregulation of the MAOA signalling pathways. Ultimately, it impairs the metabolism of serotonin and related neurotransmitters, creating a vicious cycle. Furthermore, the reduced HAAO and AADAT expressions within the TRP pathways have been shown to affect NMDA activation and neuroprotection. In this regard, it can be suggested that nutrient insufficiency associated with stereotyping eating patterns in ASD is secondary to multiple central regulatory mechanisms. This includes hyperserotoninaemia, which causes well-known effects on motility, intestinal fluid secretion and absorption, and local immune regulation. These result in the suppression of excitatory signalling and the emergence of typical ASD symptoms. Manifestation includes negative signs as reduced exploratory behaviours, diminished emotional abilities, deficits in visual and acoustic faculties, altered perceptions, and a decline in locomotor activity and accompanying BDNF elevation.

BDNF is a neurotrophin that promotes CNS development and growth as well as neuronal survival and proliferation. It affects dopaminergic and serotonergic transmission as well as the plasticity of GABAergic and glutamatergic synapses [142-146]. In contrast, in major depressive disorder BDNF levels are significantly decreased while IGF-1 levels are increased [147]. This could suggest that neurodegeneration is predominant in ASD, and that elevated levels of adaptive BDNF are directed towards stimulating neuron progenitor cells. Given this point, it is critical to clarify whether the rationale for measuring serotonin, tryptophan, IGF-1 and BDNF could have diagnostic value regarding the multiple functional deficits associated with ASD. The above data support the use of some substances that modulate serotonin regulation, besides conventional serotonin reuptake inhibitors. Modulation of neurotransmission is closely related to folate, it concerns 5-HT, dopamine (DA) and norepinephrine (NA) and it plays an antidepressant-like role in several pathways involving monoamines. Folic acid treatment significantly increased norepinephrine and dopamine levels while regulating β-endorphin, BDNF, β-endorphin and homocysteine levels under unpredictable stress experimental conditions [148]. Most people with ASD produce folate receptor antibodies (FRA), which block the uptake of cerebral folate and result in folate deficiency in the brain [149]. In 83% of cases, the etiology of CFD in ASD was attributed to FRA, and in 43% to mitochondrial dysfunction. A meta-analysis found that FRA were detected in 71% of cases of ASD, with no significant variation observed across studies. Children diagnosed with ASD exhibited a 19.03-fold elevated likelihood of positivity for a FRA when compared to controls. Folinic acid (*d,l*-leucovorin) usage is associated with improvements in core and associated symptoms in 67% of ASD patients concerning irritability (58%), ataxia (88%), pyramidal signs (76%), movement disorders (47%), and epilepsy (75%) [150].

Vitamin B6 is a key factor in the regulation of melatonin, DA, 5-HT, NE and GABA synthesis. Even mild deficiency could lead to reduced GABA and serotonin and affect sleep, behaviour, and a loss of hypothalamus -pituitary control [151]. Supplementation with B6 reduced anxiety and was more pronounced for generalised anxiety disorder symptoms [152]. Hence, adding vitamin B6 and folic acid to serotoninergic modulation might be an option in changing of serotonin, tryptophane, and BDNF in patients with ASD.

A considerable body of literature delineates the relationships between OXT, 5-HT, GABA and DA. OXT exerts its influence over GABAergic neurons by

activating neurogenesis and neurodevelopment. Recent meta-analyses and review studies have emphasised that reduced concentrations of OXT in the blood may be associated with ASD [153]. Concurrently, an inverse OXTR distribution between nucleus basalis and ventral pallidum results in altered cortico-striatal connectivity and could produce typical signs of sensorial hyporeactivity with unusual visual attention. At the same time, DNA methylation serves as a key regulator of gene expression, including pathways associated with ferroptosis and peroxidation. Furthermore, we have noted the importance of DNA methylation when considering oxytocin regulatory pathways, particularly in blunting of the OXTR protomer (Fig. 5). OXTR hypermethylation in children diagnosed with ASD could result in diminished OXT concentration, which results in impairment of GABA, 5-HT and DA. The study of methylation state (e.g., folic acid genes) and OXT levels may hold diagnostic significance in patients with ASD with sensory deficits and attention disorders. In a randomised, placebo- controlled study, four weeks of long-term OXT administration stimulated oxytocin synthesis in children with ASD. It was confirmed by elevation of OXT level in saliva and decreased methylation of OXTR with clinically evidenced improved feelings of secure attachment [154]. Meta-analysis found the significant effect of OXT with administration of 48 IU per day on social impairments and repetitive behaviour [155]. Thus, the most recent studies provide evidence for an option for intranasal OXT treatment in ASD.

NMDARs, which are widely distributed in the cortex, regulate the plasticity of synapses and are important for prolonged potentiation and depression. It represents the cellular mechanisms that underlie memory and learning processes as well as excitotoxicity leading to neuronal death, a phenomenon observed in various neurodegenerative diseases [156].

Decreased empathy in ASD is associated with low neurite density index in left prefrontal cortices, as shown by voxel-wise GM-based spatial statistics analysis [157]. It was shown that in patients with ASD, the total level of N-acetyl-aspartate was decreased in the putamen and insula, while in the hippocampus, the glutamate concentrations were significantly increased, which is related to reduced neuronal or axonal density and impaired mitochondrial metabolism [158]. At the same time, a significant increase in neuron-positive polymorphic density was observed in the subplate zone of the cortex in ASD, based on postmortem tissue analysis. These data could be evidence of neuronal underdevelopment and immaturity [159]. Thus, the elevated levels of NMDARs in patients with ASD could be related to increased neuronal density in the cortex, resulting from damaging factors in the intrauterine period that affect neuronal “pruning” and disrupt cortico-cortical and cortico-striatal projections.

Prenatal zinc deficiency is another non-genetic model of ASD, which is causally linked to impairments such as memory and learning deficits, as demonstrated in animal models [160]. Transsynaptic mobilisation of Zn promptly reverses social interaction deficits in mice with ASD in two independent experimental models. Postsynaptic Zn elevation is stimulated by Zn chelator and ionophore clioquinol, resulting in improved social interaction in mice with experimental Shank2 scaffolding protein deficiency. NMDARs modulation is driven largely by presynaptic Zn release, activating the postsynaptic tyrosine kinase-dependent pathway [161, 162]. Non-competitive NMDA receptor antagonists include cerestat, phencyclidine, ketamine, magnesium preparations, dextromethorphan, dextrorphan, disolcipine, and remacemide, which bind to the phencyclidine site on NMDA-associated ion channels [163-166]. The excitor/inhibitory imbalance in mice with prenatally valproic acid-induced ASD-like behaviour was associated with 5-HT receptors hypo-signalling and decreased by 5-HT1A receptor agonist [167].

Magnesium has also been demonstrated to block NMDA-dependent channels in a potential-dependent manner. The way Mg2+ associates with the Zn^{2+} pocket of the GluN2-NTD subunits results in allosteric inhibition of NMDARs channel activity. Magnesium is a key regulator of NMDARs, making them coincidence detectors for excitatory synaptic transmission, playing a vital role in supporting brain development and driving synaptic plasticity [168]. Magnesium exerts neuroprotective effects by mitigating oxidative damage and suppressing inflammatory responses. In healthy individuals, higher magnesium consumption is directly associated with improved cognitive outcomes [169].

Extensive evidence confirms that glycine serves as a fundamental inhibitory neurotransmitter across various CNS structures. The role of glycine as an inhibitory neurotransmitter has been demonstrated in almost all parts of the CNS. The density of glycine receptors is increased in the brain. A high density of glycine receptors is found in the cerebral cortex, striatum, hypothalamus and brainstem, and conduits from the frontal cortex to the hypothalamus and cerebellum. For glutamate NMDA receptors to function optimally, the presence of glycine in submicromolar concentrations is required, as established by various experi- mental models. The activation of NMDA receptors necessitates the binding of glycine to its designated sites, i.e. glycine is required to function as their co-agonist. Acting via NMDA receptor sites, glycine substantially mitigates programmed cell death within the neuronal population. Co-administration of glycine with glutamate and NMDA within the culture medium was found to both decrease neuronal death and impact the morphological type of death, switching it from necrosis to the less dangerous apoptosis. All this makes a perspective for ASD-targeted therapy [170-172].

The metabolic pathway for synaptic glycine involves its production via serine hydroxymethyltransferase, an enzyme whose activity depends on the dual participation of tetrahydrofolate and pyridoxal phosphate. The enzymatic generation of glycine in the CNS is primarily driven by glycine synthase (GCS) enzyme, which orchestrates a reversible interaction between various substrates, including ammonium ions, carbon dioxide, and methylene tetrahydrofolate, with NADH and a proton exchange. This enzymatic pathway concludes with the resultant production of glycine, tetrahydrofolate and NAD+ [173]. It is highly probable that folate acts as a key modulator of glycine signalling, offering a potential metabolic target for patients with ASD.

Scaffolding SHANK proteins (e.g., SHANK3) have a crucial significance in the integrated development of the CNS prenatally. Findings indicate that SHANK3 fulfils a pivotal developmental function in regulating intrinsic neuronal excitability in human neurons. These proteins have been identified specifically at neuronal postsynaptic densities. In these loci, it serves as an organising centre, regulating the complexity of postsynaptic signal transduction. Mutations affecting SHANK3 expression or function cause neurodevelopmental deficits primarily by impairing synaptic activity. Increases in cortical activity occurring at an early stage in Shank3B-/- mutant mice are related to premature maturation of striatal projection neurons and corticostriatal connectivity [174].

Patients with SHANK3 mutations are characterised by a severe cognitive deficit. SHANK3 heterozygous mutations have been shown to alter the glutamate transport in synapses. These mutations in different exons induced ASD -like clinical signs, such as anxiety, diminished social interaction and compromised motor coordination. SHANK mutant mice show specific ASD-like phenotypes due to NMDAR hypofunction [175]. Consequently, altered SHANK proteins may induce adverse consequences on postsynaptic transmission, synaptic connections and neuronal networks, affecting NMDA neurons, potentially exacerbating the cognitive impairments observed in ASD. Therefore, based on the synthesised evidence, a comparison was made between the clinical data characteristic of the ASD, corresponding biomarkers and modulating agents. While ferritin and transferrin concentrations show quantifiable disparities among the ASD population, their clinical relevance remains understated due to weak correlations and limited evidence.

Among immune and inflammatory biomarkers, the elevation of NSE, detected in 97.5% of pediatric patients with ASD, may be linked to underlying neuronal metabolic stress and impaired neurodevelopment. Current evidence supports its consideration as a sensitive biomarker of neuronal activity in ASD, though validation is required [131, 176, 177]. Glutathione and MDsdA elevation were found as the biomarkers of peroxidation stress that are most frequently reported in ASD [178-180]. Roughly 40% of children with ASD exhibit increased circulating serotonin concentration. Despite not being concordant with symptom severity, this hyperserotonemia is considered relevant to early neurodevelopment and shows inverse association with oxytocin release, indirectly modulating social behaviour [181]. As a central mediator of neuroplasticity, BDNF has a crucial significance in the development of the CNS. Findings suggest that diminished BDNF levels in pediatric ASD cases correlate with more pronounced clinical manifestation, potentially impacting cognitive, linguistic and interpersonal development. These data advocate for the consideration of BDNF as a biomarker in specific ASD subgroups [182, 183].

Anti-folate receptor antibodies have been detected in 70% of pediatric patients with ASD. Treatment with oral folinic acid in these groups was linked to positive outcomes, regarding speech, language proficiency and social interaction. Treatment with oral folinic acid was associated with improvements in language, speech, and social interaction. This biomarker holds potential value for diagnosis as well as for monitoring therapy [184, 185]. Accordingly, Table 2 presents the suggested biomarkers and the potential modulatory agents for therapeutic consideration. As shown in Table 2, there is a relatively new class of FDA-approved recombinant and synthetic IGF-1 derivative analogue biopreparations that could be utilised in several syndromal characteristics of ASD [186]. On the other hand, a safe and pathogenetically determined combination of certain substances could produce a potentiating effect. However, this depends both on the prominence of certain ASD characteristics and on the scale of biomarkers in a particular patient, which allows the dosage and regimen to be adjusted. Furthermore, the integration of ASD pharmacotherapy with supportive therapies, such as sensory integration, has demonstrated greater therapeutic potential in pediatric cases. A significant therapeutic benefit is also observed with those receiving treatment demonstrating greater proficiency in daily activities and an upgraded quality of life. It should also be emphasised that the efficiency of the multidisciplinary approach in ASD management. The reversal of level 3 severity of autism in dizygotic female twins was realised due to a parent-driven, multidisciplinary, therapeutic approach involving licensed specialists, with a focus on lifestyle modification, which was demonstrated. This intervention was personalised to each twin's symptoms, laboratory data, and other outcomes [187, 167]. Sensory hyperreactivity may be interlinked with diverse patterns of sensory modulation impairment within the ASD population. Structurally and functionally, the thalamus exerts a fundamental influence in multimodal sensorimotor prcessing. Research reveals that increased thalamic

Table 2. Prevailed ASD signs, suggested biomarkers, and potentially associated modulatory substances.

Prevailed ASD signs	Suggested biomarkers	Suggested modulation
History of prenatal viral exposure, DSM-5 relevant signs of DA deficit (unusual mood or emotional reactions, anxiety, stress, or excessive worry)	Retinoid status, (w) dopamine, IgG antibodies to DA1 and DA2 receptors, (w) BDNF9 (m), IGF-1(m), NSE (m), oxidative stress markers (m), (malonic dialdehyde)	Folinic acid (leucovorin or L-methylfolate) or all-trans retinoic acid (p), antioxidants (glutation +Vit C + NAC), IGF-1 derived neurotrophins (s), (mecasermine, trofinetid)
Parasomnias, restless legs syndrome, delayed language skills, DA deficit	Ferritin, transferrin (w), dopamine (w), IgG antibodies to DA1 and DA2 receptors (w), oxidative stress markers,Vit B6 levels (w), NSE (m), HSP(w)	DA agonists, antioxidants, Vit B6 (c)
Negative DSM-5 relevant signs (avoids or does not keep eye contact, does not respond to name by 9 months of age, does not show facial expressions such as happy, sad, angry, and surprised by 9 months of age)	Serotonin (m), BDNF (m), IGF-1 (m), tryptophan (w), folates (m), Vit B6 levels (w)	SSRI (s), folinic acid, Vit B6 (p)
DSM-5 relevant repetitive signs (focusing on parts of objects, obsessive interests, extreme interest or knowledge of specific, narrow topics, strong attachment to a certain object)	Oxytocin(m), folic circle genes (w), folates (w), Vit B6 levels (w)	Intranasal oxytocin (c), folates (p), Vit B6 (p), neurotrophins (s)
DSM-5 relevant cognitive signs (delayed cognitive or learning skills, hyperactive, impulsive, and/or inattentive behaviour)	Plasma glutamate, magnesium, zinc (w), NSE (m), BDNF(m), IGF-1(m)	NMDARs antagonists, glycine (s), magnesium-containing drugs (s), zinc-containing drug (s)

Notes. Evidence strength for biomarkers: w-weak, m-moderate, s-strong. Evidence strength for modulators: s-speculative, p-preclinical, c-clinical.

connectivity and altered function of the auditory, visual and olfactory cortices take place in ASD [188].

The serotonin system is the earliest brain-developing signal system. Evidence suggests that 5-HT is fundamental to in-utero programming, a process that establishes differential susceptibility to both adverse and favourable life events. Such sensitivity has been demonstrated to correlate with a predisposition to chronic behavioural and psychiatric complications later in life [189]. In this context, the early prenatal environment may exert an influence on 5-HT regulation, with potential implications for other signaling systems and thalamocortical connectivity with the potential to cause disorders in sensory integration, a core manifestation of ASD Fig. 6. Shows an example of a possible mechanism of integration of signaling pathways under prenatal viral effects on the CNS, leading to the subsequent development of ASD-associated symptoms.

Pharmacological agents such as probiotics, mitochondrial cofactors, anti-inflammatory compounds, and metabolic modulators have demonstrated potential in targeting the fundamental pathophysiological mechanisms present in ASD. Their actions may involve modulation of oxidative stress, mitochondrial respiration, synaptic plasticity, and mTOR signaling, which are involved in ASD pathogenesis [190, 191]. A personalised approach that integrates genetic testing, biomarker profiling, and functional clinical assessment is crucial for target therapy and for treatment results in children with ASD [192, 193]. It should also be noted that most suggested modulatory agents lack adequate clinical validation. Consequently, they represent promising research directions aimed at clarifying their relevance to ASD symptoms, with particular importance in the pediatric population.

Conclusion

This review outlines several pathogenetic mechanisms linked to the manifestations of autism spectrum disorders. It highlights that prenatal exposure to viral agents significantly contributes to irreversible changes in neural architecture, where the specific neurologic outcome is directly linked to the viral profile involved.

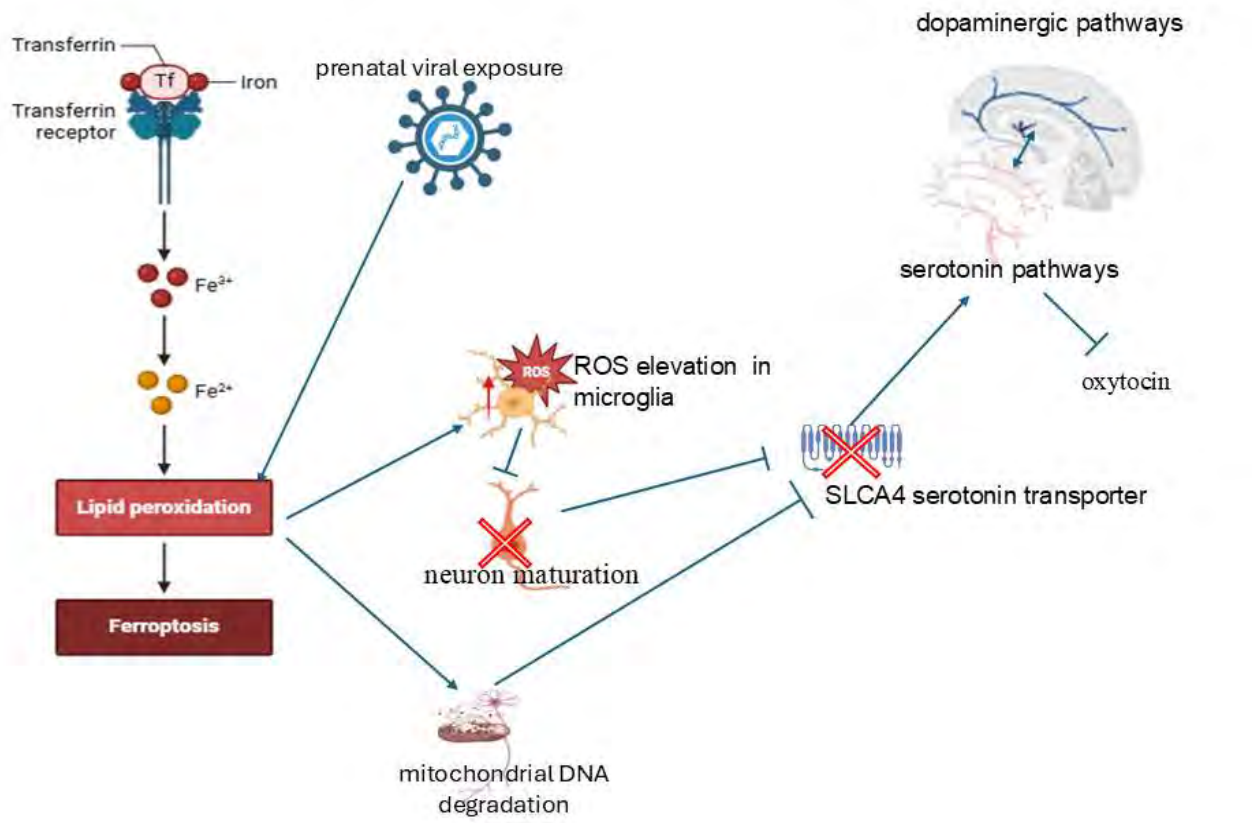

Figure 6. Suggested cohesion of signaling pathways leading to ASD symptoms following prenatal viral exposure.
Prenatal viral insult and immune activation induce lipid peroxidation, which drives ferroptosis and mitochondrial degradation, ultimately impairing neuronal maturation. Consequently, failure of neuronal maturation results in serotonin transporter damage, perturbing serotonin–dopamine and serotonin–oxytocin interactions. This cascade underlies ASD-related manifestations such as low social responsiveness, altered visual attention, and reduced motivated behaviour.

For example, the rubella virus is linked to disrupted retinoic acid metabolism; CMV is linked to impaired neuronal progenitor formation, dysfunction of excitatory and inhibitory processes, inhibition of dopaminergic synaptic pathways, and impaired neuronal growth. HSV exposure contributes to mitochondrial DNA degradation and microglial hyperperoxidation. Intrauterine infection with SARS-CoV-2 is related to reduced concentrations of IGF-1 and CNS demyelination. Influenza virus is associated with the suppression of cortical neurogenesis, neuronal lamination, and radial migration. Collectively, these processes contribute to neurodegeneration and the postnatal manifestation of ASD symptoms. The review also highlights the significance of ferroptosis and its impact on iron metabolism and immune activation in ASD, associated with the level of manifestation and clinical symptoms such as restless legs syndrome, parasomnias, dopamine deficiency and delayed language skills. Dysregulation of serotonin signaling pathways is shown to underlie several negative symptoms in ASD, including visual, locomotor, and emotional deficits. Deficits in oxytocinergic neurotransmission exacerbate social challenges and induce a mismatch between motivational behaviour and visual focus, which suggests OXTR-gene hypermethylation as a possible epigenetic driver of these symptoms. Furthermore, impaired oxytocin signaling contributes not only to social deficits but also to a dissociation between motivational behaviour and visual attention, potentially associated with altered methylation of the OXTR gene. Deficiencies in NMDA- mediated neurotransmission are linked to neurocognitive challenges of ASD, manifesting as delayed educational skills and pronounced hyperactive-impulsive phenotype. The clinical and pathogenetic correlations identified through the literature analysis, particularly those involving gene signaling regulation, provide a foundation for the identification of potentially relevant biomarkers. These findings may provide a foundation for combined modulation approaches offering a promising avenue for precision therapeutic strategies in ASD.

Conflicts of Interest

The authors declare no conflict of interests.

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ШЛЯХИ ГЕННОЇ СИГНАЛІЗАЦІЇ, ПУТАТИВНІ БІОМАРКЕРИ ТА ГІПОТЕТИЧНА МОДУЛЯЦІЯ ПРИ РОЗЛАДАХ АУТИСТИЧНОГО СПЕКТРА

Розлад аутистичного спектра (РАС) є одним із найпоширеніших неврологічних порушень, із постійним зростанням поширеності. Наведено теоретичне обґрунтування для визначення потенційно клінічно значущих діагностичних біомаркерів та можливостей цільової фармакологічної модуляції на основі сучасних даних про генно-сигнальні шляхи. Це систематичне оглядове дослідження базується на даних систематичних оглядів та мета аналізів, присвячених базовим аспектам розладу аутистичного спектра. Це дозволило окреслити підходи до синдром-асоційованої діагностики та терапевтичних стратегій. У статті розглянуто інтегративні патогенетичні механізми РАС, що охоплюють пренатальний вірусний вплив, зміни у серотонінових та окситоцинових сигнальних шляхах, регуляцію N-метил-D-аспартатних рецепторів, білків SHANK та представників родини Solute Carrier. Імунні, вірусні та метаболічні чинники, нейромедіаторні системи, синаптичні білки та структурна регуляція, біомаркери й терапевтичні стратегії визначені як перспективні для діагностики та модуляції при РАС. Показано перспективність комбінованої модуляції із залученням похідних ретиноєвої кислоти, фолатів, антиоксидантів, нейротрофінів, препаратів окситоцину, гліцину та магнію залежно від синдромальної маніфестації РАС. Встановлено можливу роль вірусу краснухи у пренатальному порушенні метаболізму ретиноєвої кислоти та подальшому порушенні формування нейронних шляхів, а також специфічний вплив вірусу COVID-19 на сигнальний шлях IGF-1. Припускається взаємозв'язок аутоімунної активації при порушенні дозрівання нейронів із процесами фероптозу, результатом чого є зниження рівнів феритину та трансферину у дітей з РАС. Аналіз літератури засвідчує потенціал більш селективної діагностики та модуляції РАС із використанням специфічних біомаркерів та окреслює напрями майбутніх досліджень.

Ключові слова: розлад аутистичного спектра; генно-сигнальні шляхи; трансферин; феритин; серотонін; окситоцин; фармакологічна модуляція.