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Review

A review of glycolysis and autism spectrum disorder: The dual role of lactic acid in neurodevelopment and function

Ziqing Jiang[1], Yingxin Zhou[1], Peiqun Liu[2], Yiying Zhou[1], Yuxuan Gao[3], Qin Fan[1,*], Jintao Lin[4,*]

[1] School of Traditional Chinese Medicine, Southern Medical University, Guangzhou 510515, China
[2] School of Traditional Chinese Medicine, Guangdong Pharmaceutical University, Guangzhou 510006, China
[3] Department of Orthopaedics, Shenzhen Pingle Orthopedics Hospital, Pingshan District Hospital of Traditional Chinese Medicine, Shenzhen 518188, China
[4] Nanfang Hospital, Southern Medical University, Guangzhou 510515, China
*** Corresponding authors:** Qin Fan, fqin@163.com; Jintao Lin, linjintao131@163.com

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Abstract: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental disorder characterized by impairments in social interaction, communication, and repetitive behavioral patterns. ASD is often accompanied by metabolic abnormalities, dysregulation of the immune system, and neuroinflammation. Glycolysis, a central pathway in energy metabolism, is vital for neurodevelopment and functioning. Recent studies have indicated that patients with ASD may experience disturbances in brain metabolism, particularly in the glycolytic pathway, with abnormal lactic acid production and utilization. Lactic acid serves not only as an energy source for cellular functions but also plays a significant role in cell signaling, gene expression regulation, and immune modulation. This review examines the mechanisms of glycolysis, especially the role of lactic acid in ASD; explores the relationship between lactic acid accumulation and neuroinflammation, neuroplasticity, and neurotrophic factors; and discusses the potential of lactic acid as a diagnostic and therapeutic target for ASD. Future research on modulating lactic acid metabolism may offer new strategies for the early diagnosis, precise treatment, and neural repair of ASD.

Keywords: autism spectrum disorder; glycolysis; lactic acid accumulation; neurological function

1. Introduction

Autism Spectrum Disorder (ASD) is a heterogeneous neurodevelopmental condition characterized by core deficits in social communication, restrictive repetitive behaviors, and atypical sensory processing. According to the DSM-5 diagnostic criteria, an ASD diagnosis requires persistent impairment across two functional domains: (1) Social-emotional reciprocity and non-verbal communication and (2) inflexible adherence to routines or hyper/hyporeactivity to sensory input [1]. These symptoms typically emerge during early childhood, imposing substantial lifelong challenges on the affected individuals and their caregivers.

Global epidemiological studies have revealed a rising prevalence of ASD, currently affecting approximately 1% of the pediatric population, with pronounced male predominance (male-to-female ratio of 4:1) [2]. While precise etiopathogenesis remains elusive, converging evidence implicates multifactorial interactions involving neuroimmune dysregulation, alterations in the gut-brain axis, polygenic susceptibility, and deficits in synaptic plasticity [3–5]. Neurobiological investigations have highlighted abnormalities in activity-dependent neural circuit formation, with

particular emphasis on perturbations in the excitation-inhibition (E/I) balance mediated by deficiencies in γ-aminobutyric acid (GABA) signalling [6,7]. Notably, Yoshida et al. demonstrated that soluble Lingo2 (sLingo2) protein promotes excitatory synaptogenesis in murine and human neuronal models, as evidenced by the increased miniature excitatory postsynaptic current frequency following sLingo2 administration [8]. Of particular concern is that patients with ASD often exhibit metabolic abnormalities and immune system dysregulation [9] and neuroinflammation [10], which provide important clues for revealing its pathological mechanisms. Metabolomic studies have found that patients with ASD have abnormalities in amino acid metabolism, especially in branched-chain amino acid and glutamate metabolism, which can lead to disorders in neurotransmitter synthesis, thereby affecting neural transmission and synaptic plasticity [11]. Abnormal metabolism of glutamate, the primary excitatory neurotransmitter in the brain, can affect the normal function of neural networks, and some key enzymes in the glycolytic pathway are closely related to the synthesis and metabolism of glutamate [12]. Studies have also found that patients with ASD have certain immune function abnormalities and that glycolysis may promote neuroinflammatory responses by altering the metabolic state of immune cells, thereby affecting neurodevelopment [11]. In ASD cases and controls, apolipoprotein E and EH domain-containing protein 3 are differentially expressed in the brain tissue, blood, and urine; whereas vinculin is differentially expressed in the saliva, blood, and urine [13]. In terms of pathways, glycolysis/gluconeogenesis, carbon metabolism, and glutathione metabolism were enriched in brain, saliva, or urine [13]. These studies suggested a close relationship between glycolysis and ASD pathogenesis.

The glycolytic pathway, which is fundamental to cellular bioenergetics and generation of biosynthetic precursors, is particularly relevant to neurodevelopmental processes. Maier et al. [14] reported cerebral lactate via Magnetic Resonance Spectroscopy (MRS) that the characteristics of brain metabolic reprogramming in children with ASD are manifested as alterations in glycolytic flux and lactate shuttle kinetics, resulting in abnormal elevation of brain lactate levels. In addition to its canonical role in ATP production during anaerobic conditions, lactate functions as a signalling metabolite that regulates epigenetic modifications, neuroimmune interactions, and synaptic plasticity. Therefore, exploring the roles of glycolysis and lactic acid in ASD is significant for understanding the pathogenesis of ASD and developing new intervention strategies.

This study summarizes the current knowledge on glycolytic dyshomeostasis in ASD pathogenesis, evaluates its potential as a biomarker, and discusses therapeutic strategies targeting the metabolic circuitry. By elucidating the interface between glycolysis and neurodevelopment, we aimed to advance etiological understanding and inform precision medicine approaches for ASD management.

2. Glycolysis in brain development

The human brain, which accounts for only 2% of the total body mass, paradoxically consumes approximately 20% of the body's total energy expenditure [15]. This disproportionate energy utilization underscores the extraordinary complexity and metabolic demands of neurodevelopment. Neurodevelopmental processes encompass

a series of highly orchestrated events, including the proliferation of neural stem cells, migration of neurones, extension of dendrites and axons, formation of synaptic connections, and refinement of neural network functions. Under basal conditions, neurones are believed to rely predominantly on mitochondrial oxidative phosphorylation (OXPHOS) for adenosine triphosphate (ATP) production, with glycolysis becoming the dominant pathway only during periods of increased neuronal activity. However, recent studies have challenged this hypothesis. For instance, the absence of the glycolytic enzyme pyruvate kinase M2 (PKM2) in mice results in a shift from aerobic glycolysis to OXPHOS in the neuronal somata, culminating in oxidative damage and progressive loss of dopaminergic neurones [16]. These findings highlight the critical role of aerobic glycolysis in maintaining neuronal redox homeostasis and antioxidant capacity. Glycolysis, the central pathway of cellular energy metabolism, is indispensable in the early stages of neurodevelopment, providing a rapid energy supply and generating essential metabolic intermediates that support cell growth, division, and differentiation.

2.1. Aerobic glycolysis

Aerobic glycolysis refers to the metabolic process in which cells perform glycolysis under adequate oxygen supply, with pyruvate being subsequently utilised in the mitochondria for oxidative phosphorylation. In the context of brain neurodevelopment, aerobic glycolysis serves as a vital energy source, providing ATP while also generating a diverse array of metabolic factors. These include reduced nicotinamide adenine dinucleotide (NADH) and tricarboxylic acid (TCA) cycle intermediates that are essential for neuronal proliferation, differentiation, and functional maintenance [16]. As brain development progresses and neural function matures, reliance on aerobic glycolysis increases significantly. This metabolic pathway fuels the growth of dendrites and axons and supports the establishment of functional presynaptic and postsynaptic structures. Moreover, metabolic intermediates generated through aerobic glycolysis contribute to the synthesis of critical molecules, such as neurotransmitters, lipids, and proteins. Under conditions of elevated energy demands, aerobic glycolysis and oxidative phosphorylation operate together to sustain the complex energy requirements of neural activity.

Aerobic glycolysis plays a pivotal role in the intricate interplay between neurones and glial cells. Given that a portion of the neuronal energy demand is met by glial cells, an efficient glial glycolytic mechanism metabolizes glucose into lactate, which is then transported to neurons to generate ATP via the neuronal TCA cycle. This process is described by the astrocyte-to-neuron lactate shuttle (ANLS) hypothesis [17], which was proposed by Pellerin and Magistretti in 1994 and aims to explain the coupling mechanism between neural activity and energy metabolism. This hypothesis posits that during neuronal excitation, astrocytes uptake synaptic glutamate via a glutamate-dependent mechanism, which activates intracellular glycolytic pathways to produce lactate. Subsequently, lactate is released into the extracellular space through monocarboxylate transporters (MCTs) and is taken up by neurons to serve as the primary energy substrate for oxidative metabolism. Experimental evidence has demonstrated that a deficiency in lactate production by adenosine monophosphate-

activated protein kinase (AMPK)-deficient astrocytes leads to neuronal loss [18]. Metabolic coupling is essential for maintaining synaptic homeostasis and facilitating efficient neural signal transmission. The functional metabolic flexibility of aerobic glycolysis during early neurodevelopment supports the rapid tissue growth and cell differentiation required for proper brain development [19].

2.2. Anaerobic glycolysis

Anaerobic glycolysis is the process by which cells generate energy and convert pyruvate into lactate under conditions of limited oxygen availability or localized high metabolic demand. During the early stages of brain neurodevelopment, incomplete formation of the blood-brain barrier and rapid proliferation of nerve cells often result in insufficient oxygen supply, rendering anaerobic glycolysis the primary pathway for energy acquisition [20]. This rapid energy supply provides the necessary ATP for cell proliferation and migration, whereas lactate, the primary byproduct of anaerobic glycolysis, serves as an important signalling molecule in neurodevelopment. Recent studies have shown that lactate activates key signalling pathways, including hypoxia-inducible factor-1 alpha (HIF-1α) [21], AMPK [22], and mammalian target of rapamycin (mTOR) [23], thereby promoting neuronal growth, axon guidance, and synapse formation [24]. Lactate also circulates between neurones and glial cells, maintaining homeostasis of neuronal energy metabolism [25].

Furthermore, the metabolic intermediates of anaerobic glycolysis can influence cell fate decisions by modulating histone lactylation and epigenetic states, thereby affecting neuronal differentiation and migration [26].

3. Mater glycolysis and the potential relationship with ASD

3.1. The Warburg effect and lactate accumulation in ASD

The Warburg effect, also known as aerobic glycolysis, is a metabolic reprogramming characterized by increased glycolysis and lactate production even in the presence of oxygen, and it is associated with various pathological states, including ASD [27]. This phenomenon, first described by Otto Warburg in the 1920s, is driven by enhanced glycolytic enzyme expression, increased glucose transporter activity, and altered mitochondrial function [28]. In the context of ASD, the Warburg effect leads to excessive lactate accumulation, which can induce neurotoxicity and neuroinflammation, contributing to the pathogenesis of the disorder.

Lactate, once considered a mere byproduct of glycolysis, is now recognized as a critical energy source and signaling molecule in the central nervous system (CNS) [19]. It can be transported from astrocytes to neurons via the ANLS, providing a vital energy substrate that supports neuronal activity and synaptic plasticity [17]. However, excessive lactate accumulation can lead to neurotoxicity and neuroinflammation, which may contribute to the development of ASD. The Warburg effect exacerbates this issue by increasing lactate production and accumulation, creating an environment that promotes neuroinflammation and neuronal dysfunction.

The Warburg effect influences lactate accumulation in ASD through several mechanisms. Firstly, it activates microglia and astrocytes, leading to the release of pro-

inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and interleukin-1β (IL-1β) [29]. These cytokines can exacerbate neuroinflammation and contribute to the development of ASD. Secondly, lactate can induce epigenetic changes through lactylation, a post-translational modification that involves the addition of a lactate group to lysine residues on proteins. Lactylation can modulate gene expression and chromatin structure, affecting neuronal function and development. Lastly, lactate can influence neurotransmitter systems, such as glutamate and GABA [12], which are critical for neuronal communication and synaptic plasticity. Dysregulation of these neurotransmitter systems has been implicated in ASD.

In addition to these mechanisms, the Warburg effect can also significantly impact mitochondrial function in ASD. This metabolic reprogramming leads to excessive lactate accumulation, which can induce neurotoxicity and neuroinflammation, contributing to the pathogenesis of ASD. The Warburg effect results in decreased activity of mitochondrial complexes, particularly complex I, which is crucial for the electron transport chain (ETC). This reduction in complex I activity leads to decreased ATP production and increased oxidative stress. Post-mortem studies of autistic brain samples have shown abnormal changes in the steady-state levels of complexes I-IV in various brain regions, including the cingulate gyrus, cerebellum, thalamus, and temporal and frontal cortex. The dysfunctional ETC associated with the Warburg effect leads to increased reactive oxygen species (ROS) production. These ROS can damage mitochondrial components, including lipids, proteins, and DNA, further impairing mitochondrial function. The overproduction of ROS creates a vicious cycle, leading to progressively increasing damage to the mitochondria, which may ultimately result in cell death [30].

In summary, the Warburg effect plays a significant role in autism induced by lactate accumulation by promoting neuroinflammation, epigenetic modifications, altered neurotransmitter function, and mitochondrial dysfunction. Future research should delve into the specific mechanisms by which the Warburg effect is involved in the pathogenesis of ASD and focus on developing targeted therapeutic approaches that modulate lactate metabolism and reduce lactate accumulation, offering promising treatment strategies for ASD.

3.2. Glycolysis and metabolic abnormalities in ASD

In addition to aerobic glycolysis, the aberrant activation of anaerobic glycolysis has been implicated in neurodevelopmental disorders, including ASD. Clinical studies have consistently demonstrated that a significant proportion of individuals with ASD (approximately 43.4%) exhibit lactic acidemia [31], a finding that has been replicated in multiple investigations (**Table 1**) [32,33]. This prevalence suggests an increased reliance on anaerobic metabolic pathways in neurones associated with ASD, which is characterized by excessive glycolytic activation leading to lactate accumulation. In addition to serving as an energy substrate, lactate plays a crucial role in regulating cellular metabolic homeostasis and neuronal function through its impact on various signalling pathways. Studies have shown that lactate serves as a key modulator of synaptic plasticity and neuronal excitability through its agonistic action on the G protein-coupled receptor Hydroxycarboxylic Acid Receptor 1, which suppresses

intracellular cyclic adenosine monophosphate (cAMP) synthesis. This suppression dynamically regulates neuronal network adaptability [34]. Concurrently, lactate exerts epigenetic modulation by antagonizing histone deacetylases (HDACs), thereby elevating histone acetylation levels. Such epigenetic remodeling orchestrates transcriptional programs critical for synaptogenesis and the consolidation of long-term memory [35]. Excessive lactate accumulation may be intricately linked to the clinical manifestations of ASD, including behavioral anomalies and cognitive impairment. Empirical clinical investigations have elucidated a marked elevation in cerebrospinal fluid (CSF) lactate concentrations among individuals diagnosed with ASD, with quantitative correlations observed between hyperlactatemia and the severity of core behavioral phenotypes [36]. Pathologically sustained lactate accumulation may potentiate bioenergetic derangements through allosteric inhibition of pyruvate dehydrogenase (PDH) complex activity, thereby disrupting neuronal oscillatory synchrony and precipitating maladaptive behavioral manifestations, including aberrant social interaction and compromised cognitive flexibility [37]. Notably, a hyperlactatemic microenvironment selectively impairs mitochondrial oxidative phosphorylation in GABAergic interneurons, diminishing γ-aminobutyric acid (GABA)-mediated inhibitory tone and consequently inducing a pathological excitation-to-inhibition (E/I) ratio imbalance—a canonical pathophysiological cascade underlying sensory hyperarousal and socio-communicative deficits in ASD [38].

Table 1. Clinical research in past years.

Title	Author	Year	Sample Type	Sample Size	Change of Lactate acid level
Autism and lactic acidosis	M Coleman	1985	Blood and unrine	4	Increased
Clinical heterogeneity of the autistic syndrome: a study of 60 families	H Moreno	1992	Plasma	60	Increased
Evidence of altered energy metabolism in autistic children	D C Chugani	1999	Plasma	15	Increased
Mitochondrial dysfunction in autism spectrum disorders: a population-based study	G Oliveira	2005	Plasma	120	Increased
Mitochondrial disease in autism spectrum disorder patients: a cohort analysis	Jacqueline R Weissman	2008	Plasma	25	Increased
Metabolic biomarkers related to energy metabolism in Saudi autistic children	O A AI-Mosalem	2009	Plasma	60	Increased
Mitochondrial dysfunction in autism	Ceclia Giulivi	2010	Plasma	20	Increased
Increased markers of oxidative stress in autistic children of the Sultanate of Oman	Musthafa M Essa	2012	Plasma	38	The level of lactate to pyruvate ratio increased.
Altered metabolites in the plasma of autism spectrum disorder: a capillary electrophoresis time-of-flight mass spectroscopy study	Hitoshi Kuwabara	2013	Plasma	53	Decreased

Table 1. (*Continued*).

Title	Author	Year	Sample Type	Sample Size	Change of Lactate acid level
Mitochondrial dysfunction as a neurobiological subtype of autism spectrum disorder: evidence from brain imaging	Suzanne Goh	2014	Brain (imaging)	171	Increased
The urinary 1 H-NMR metabolomics profile of an italian autistic children population and their unaffected siblings	Milena Lussu	2017	Urine	42	Decreased
Novel biomarkers of metabolic dysfunction is autism spectrum disorder: potential for biological diagnostic markers	Asama M Khemakhem	2017	Plasma	82	Reported lactate dehydrogenase is abnormal in children with ASD.
Higher Lactate Level and Lactate-to-Pyruvate Ratio in Autism Spectrum Disorder	Miae Oh	2020	Peripheral blood	195	Increased.
Association Between Plasma Metabolites and Psychometric Scores Among Children With Developmental Disabilities: Investigating Sex-Differences	Jennie Sotelo-Orozco	2020	Plasma	442	Increased
Case report: One child with an autism spectrum disorder who had chronically elevated serum levels of CK and CK-MB	Ping Rong	2022	Blood serum	1	Increased
Metabolomic biomarkers in autism: identification of complex dysregulations of cellular bioenergetics	Alan M Smith	2023	Plasma	708	Increased
Altered markers of mitochondrial function in adults with autism spectrum disorder	Kathrin Nickel	2023	Blood serum	144	Decreased
Increased cerebral lactate levels in adults with autism spectrum disorders compared to non-autistic controls: a magnetic resonance spectroscopy study	Simon Maier	2023	Brain (MRS)	142	Increased
Metabolic network analysis of pre-ASD newborns and 5-year-old children with autism spectrum disorder	Sai Sachin Lingampelly	2024	Dried blood spots	258	Increased

3.3. Neurobiological effects of lactate accumulation

3.3.1. Lactate accumulation and neuroinflammation

Emerging research has highlighted the frequent co-occurrence of neuroinflammation in patients with ASD, with marked activation of microglial and astrocytic cells [4]. Lactate accumulation has been shown to activate neuroglial cells, including astrocytes and microglia, thereby stimulating the release of pro-inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α) and interleukin-1 beta (IL-1β) [29]. Furthermore, lactate induces metabolic reprogramming in immune cells, including macrophages and T cells, which significantly enhances the secretion of pro-inflammatory cytokines. Studies have demonstrated that in murine macrophages, lactate upregulates myeloid differentiation protein 2 (MD-2), thereby

potentiating the pro-inflammatory response induced by lipopolysaccharide (LPS), a process facilitated by lactate transporters (monocarboxylate transporters, MCT) [39]. Additionally, lactate modulates T cell effector functions, particularly by promoting the differentiation of the Th17 cell subset and secretion of interleukin-17 (IL-17), further amplifying the pro-inflammatory effects [40]. Elevated levels of these inflammatory cytokines exacerbate local neuroinflammatory responses, impair neuronal function and synaptic plasticity, and disrupt neural network stability. During neuroinflammation, lactate acts as a metabolic signalling molecule that may further potentiate inflammatory responses by activating inflammation-related signalling pathways, such as nuclear factor kappa B (NF-κB), thereby creating a vicious cycle [41].

Moreover, lactate accumulation may alter the acid-base equilibrium of cells, inducing changes in the intracellular and extracellular environments of neurones, thereby compromising the integrity and functionality of cell membranes [42]. Excessively accumulated lactate can modulate neuronal excitability [43], reduce neuronal viability, and even induce programmed cell death [44]. Concurrently, lactate modulates the permeability of the blood-brain barrier, thereby influencing the immune milieu of neural cells and exacerbating neuroinflammation.

3.3.2. Lactate accumulation and neuroplasticity

ASD has long been recognized as intricately linked to deficits in neuroplasticity. Neuroplasticity, the capacity of the brain to adapt to environmental changes and learning experiences through alterations in synaptic connections, neuronal activity, and gene expression, is essential for normal brain development. Recent studies have revealed that individuals with ASD exhibit abnormalities in synaptic connections and neural circuits during neurodevelopment, likely stemming from restricted or dysregulated neuroplasticity [45]. In the early stages of development, ASD brains display excessive synaptic formation. However, subsequent synaptic pruning processes are aberrant, leading to overconnected or dysfunctional neural networks. This phenomenon is closely tied to key molecular mechanisms, such as alterations in the BDNF and mTOR signalling pathways, which play a central role in regulating neuroplasticity and neuronal development. Collectively, abnormal neuroplasticity may be a pivotal pathological foundation for ASD onset.

Lactate accumulation significantly affects neuroplasticity, particularly during neurodevelopment and repair. Lactate, a byproduct of glycolysis, serves not only as an energy source but also as a signalling molecule involved in neuroplasticity [46]. Moderate lactate accumulation promotes neuroplasticity by activating specific signalling pathways. Specifically, lactate activates G protein-coupled receptor 81 (GPR81), thereby activating the downstream extracellular-regulated kinase 1/2 (ERK1/2) signalling pathway, which in turn regulates mitochondrial function and synaptic plasticity [47]. Studies have also demonstrated that high-intensity interval training can enhance synaptic plasticity by increasing mitochondrial number and ATP production through lactate, a process contingent upon activation of the GPR81 receptor [48]. Furthermore, lactate enhances the activity of Silent Information Regulator 1 (SIRT1), promoting neuronal survival and synaptic pruning, thereby improving synaptic plasticity and remodeling of neural networks [49]. In colon cancer

research, gentisic acid demonstrates significant inhibitory effects on lactic acid-induced EMT and mTOR signaling in CRC cells, both in vitro and in vivo, by targeting the GPR81 pathway. This implies that high-concentration lactic acid may activate the mTOR pathway [50]. Tang's research demonstrated that the mTOR pathway is hyperactivated during autism neurodevelopment; inhibiting mTOR signaling ameliorated neuronal migration defects [51]. Thus, lactate is recognized as a signaling molecule for neurons with high metabolic demands that supports neuronal growth, differentiation, and synaptic shaping by modulating cellular energy states and redox balance.

Neurotrophic factors are intrinsically associated with neuroplasticity. These factors, including BDNF, nerve growth factor (NGF), and other molecules critical for neuronal growth, survival, and function, play vital roles in neurodevelopment, neural repair, and neuroprotection [52,53]. Among them, the dysregulation of the BDNF signaling pathway is closely associated with the pathogenesis of ASD. Changes in BDNF concentration in the peripheral blood of individuals with ASD may serve as a potential biological marker for assessing the condition. Studies have found that the plasma BDNF concentration in children with ASD is significantly reduced, and the proBDNF/mBDNF ratio shows an upward trend [54]. This indicates that impaired BDNF production plays a core role in the pathogenesis of ASD, and restoring the normal expression and function of neurotrophic factors is of significant importance in the treatment of ASD. Notably, lactate regulates the expression and function of neurotrophic factors, directly or indirectly, through its involvement in neuronal metabolic regulation, activation of specific signalling pathways, and influence on gene expression. Research has demonstrated that lactate can upregulate the expression of BDNF [49,55], a key factor in neurodevelopment and neuroplasticity. Lactate promotes neuronal growth and synaptic plasticity by modulating energy metabolism and redox balance while also supporting synaptic formation and the maintenance of neural network homeostasis. However, an environment with high lactate concentrations may activate inflammatory pathways and increase oxidative stress, potentially inhibiting NGF expression and function [56]. Additionally, lactate may indirectly support neurotrophic maintenance by promoting metabolic coupling between neurones and glial cells [55]. Studies have shown that lactate shuttled through astrocytes provides energy to neurons and regulates local neurotrophic factor levels, thereby influencing neuronal function and survival.

However, excessive lactate accumulation can exert detrimental effects on neuroplasticity. Excessively high lactate levels may alter the acid-base balance inside and outside the cells, inhibiting the formation and maintenance of synaptic plasticity [42]. A high-lactate environment activates neuroinflammatory responses [57], further damaging synaptic function and neural network stability and affecting synaptic plasticity mechanisms such as long-term potentiation and depression [58]. These adverse effects can lead to functional disorders of the nervous system. Excessive lactate accumulation can also disrupt the normal expression of neurotrophic factors, thereby affecting the nervous system function. Research has shown that in the context of neurodegenerative diseases or neuroinflammation, lactate accumulation can interfere with the action of neurotrophic factors such as BDNF, leading to neuronal death and functional decline [58]. In a Parkinson's disease (PD) model, elevated

lactate levels were found to exacerbate the apoptosis of dopaminergic neurones, whereas inhibiting hexokinase 2 to reduce lactate levels alleviated neuronal apoptosis and protected motor function in PD mice [19]. Therefore, lactate is not merely a byproduct of energy metabolism but also regulates the action of neurotrophic factors in the nervous system through various mechanisms, playing a crucial role in the development, repair, and functional maintenance of the nervous system. Particularly in neurodegenerative diseases and neurodevelopmental disorders, abnormal lactate accumulation is thought to be closely associated with defects in neuroplasticity (**Figure 1**). Uncovering the molecular mechanisms underlying abnormal lactate accumulation may provide critical insights into restoring neuroplasticity, offering significant clinical therapeutic implications for diseases such as neurodegenerative conditions and neurodevelopmental disorders, including ASD.

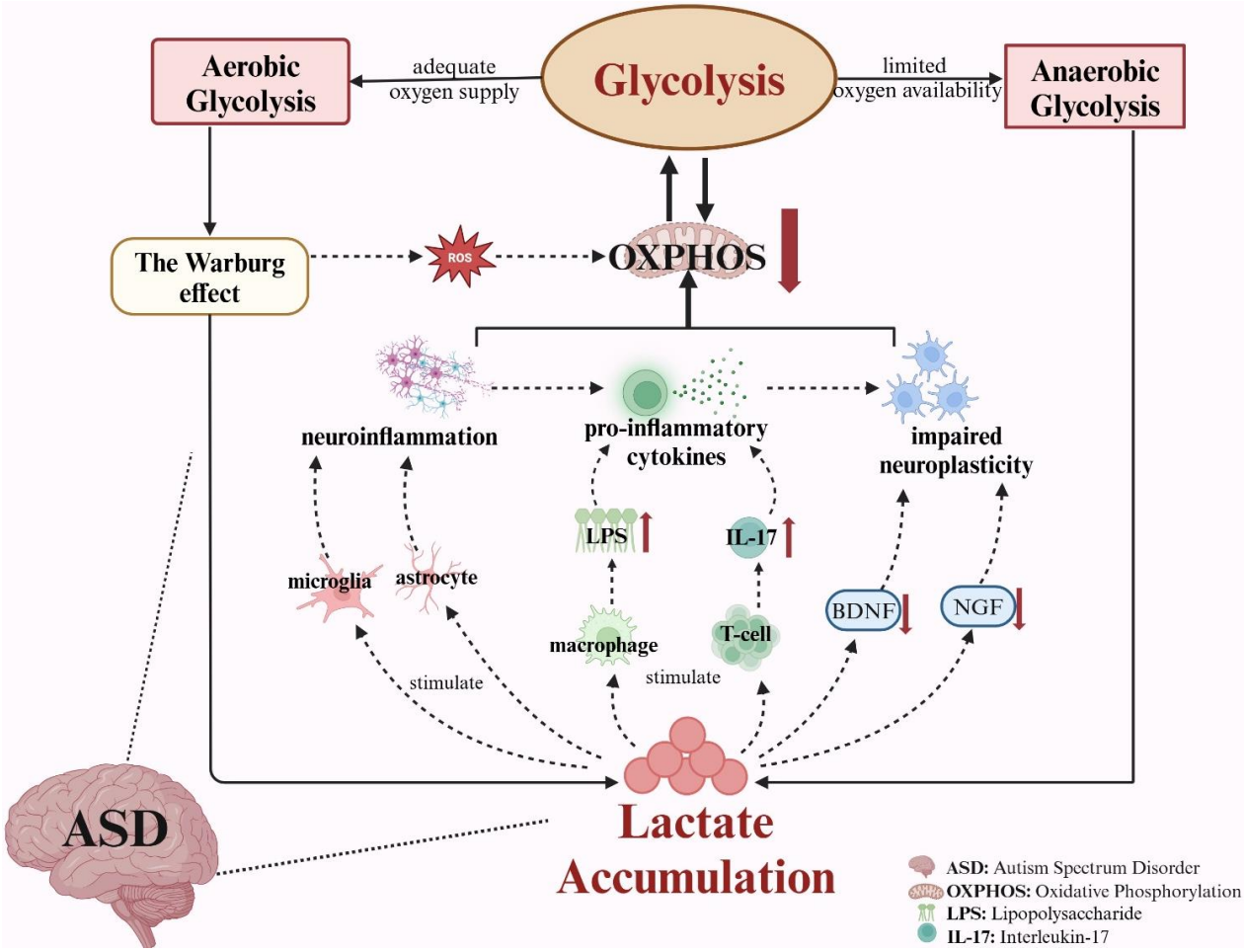

Figure 1. Essential mechanism diagram.

4. Metabolic-immune cross-talk in ASD

The excessive activation of glycolysis is intricately linked to the pathogenesis of ASD, primarily through metabolic abnormalities, neuroinflammation, and impaired neuroplasticity. The overactivation of anaerobic glycolysis leads to lactate accumulation, a condition often observed in children with ASD who exhibit hyperlactatemia. This suggests that their neurons are more reliant on anaerobic metabolism. Lactate, acting as both an energy source and a signaling molecule, may

disrupt cellular metabolic balance and neural function when accumulated excessively, correlating with ASD symptoms such as behavioral abnormalities and cognitive impairments. The accumulation of lactate can activate neuroglial cells, including astrocytes and microglia, thereby promoting the release of pro-inflammatory cytokines such as TNF-α and IL-1β [29]. Furthermore, it can induce metabolic reprogramming of immune cells, exacerbating local neuroinflammatory responses, impairing neuronal function, and synaptic plasticity. ASD is closely associated with impaired neuroplasticity, and lactate accumulation significantly impacts this process. Moderate lactate accumulation can enhance neuroplasticity by activating specific signaling pathways [20–22]. However, excessive accumulation may inhibit the formation and maintenance of synaptic plasticity through mechanisms such as altering cellular acid-base balance and activating neuroinflammatory responses [58]. This, in turn, disrupts the normal expression of neurotrophic factors, affecting the function and development of the nervous system. Therefore, the excessive activation of glycolysis is closely related to the pathogenesis of ASD.

In ASD, the metabolic-immune crosstalk is a complex and critical mechanism where glycolysis and lactate metabolism are pivotal in immune dysregulation. Research shows microglia can adapt to and modulate lactate metabolism, influencing brain physiology and pathology [59]. This metabolic shift is closely linked to neuroinflammation. When glycolysis is enhanced, microglia release more proinflammatory cytokines, accelerating their dysfunction and promoting ASD development.

Lactate, the end product of glycolysis, impacts microglial function in ASD and other immune aspects. It can inhibit indoleamine 2,3-dioxygenase 1 (IDO1) expression, reducing tryptophan metabolism to kynurenine and promoting its conversion to serotonin (5-HT), thereby influencing the neurotransmitter system and improving mood [60]. Lactate also modulates other immune cells, such as affecting T cell proliferation and cytokine production, contributing to ASD immune dysregulation. Targeting microglial metabolic pathways, especially inhibiting glycolysis, is a potential therapeutic strategy for ASD. Drugs like risperidone and aripiprazole, which modulate microglial function and suppress their activation and inflammatory cytokine production, are already used for ASD symptoms. Developing drugs that modulate lactate metabolism or affect IDO1 activity may also help improve social and emotional issues in patients with ASD.

The gut microbiota is closely related to metabolic-immune crosstalk in ASD. Probiotics and prebiotics can improve behavior in ASD children, likely due to increased lactobacilli and bifidobacteria. Synbiotics (a mix of prebiotics and probiotics) often work better than either alone, suggesting that modulating the gut microbiota to influence lactate metabolism and immune response could offer new ASD treatment ideas [61]. In conclusion, further exploring the links among glycolysis, lactate, and immune dysregulation may provide new targets and methods for ASD treatment.

5. OXPHOS/glycolysis regulatory axis

In recent years, an increasing number of studies have demonstrated a close relationship between the excessive activation of glycolysis and weakened oxidative

phosphorylation (OXPHOS) function, particularly in ASD. Patients with ASD exhibit excessive glycolysis, leading to lactate accumulation, which may be associated with impaired OXPHOS function. Research has shown that lactate levels in the cerebrospinal fluid and blood of ASD patients are significantly elevated, suggesting that their neurons are more dependent on anaerobic metabolism. This overactivated glycolysis may lead to mitochondrial dysfunction, thereby affecting OXPHOS function [36]. Because the accumulation of lactate may lead to a decrease in the NAD+/NADH ratio, which is essential for maintaining mitochondrial function and energy production. Additionally, the overactivation of glycolysis may lead to the production of ROS, which can damage mitochondrial DNA and proteins, further impairing OXPHOS function. Moreover, excessive lactate accumulation may further damage mitochondrial function through the activation of neuroinflammatory responses, creating a vicious cycle. The Warburg effect, a key metabolic characteristic of tumor cells, is characterized by a preference for glycolysis over OXPHOS for energy production even in the presence of oxygen. This metabolic reprogramming results in weakened OXPHOS function and impaired mitochondrial function. A similar metabolic reprogramming may occur in ASD, leading to mitochondrial dysfunction [62]. Some scholars have also found that restoring OXPHOS can reversibly inhibit aerobic glycolysis in an ATP-dependent manner [63]. Few tissues or cells rely solely on glycolysis or OXPHOS for energy metabolism; instead, both pathways coexist in a dynamic balance. When glycolysis is excessively activated, the proportion of OXPHOS in energy metabolism is diminished. Enhancing OXPHOS metabolism can reduce the overactivation of glycolysis, and vice versa. Therefore, we propose the existence of an OXPHOS/glycolysis regulatory axis in energy metabolism.

6. Therapeutic drugs for ASD

Given the significant roles of lactate accumulation and mitochondrial dysfunction in ASD, drugs targeting these mechanisms may hold therapeutic potential. Some known drugs, such as bumetanide and metformin, have shown certain therapeutic effects in ASD treatment. Bumetanide, a diuretic, has been used to treat ASD. Studies have shown that bumetanide can reduce core symptoms of ASD, such as social interaction impairments and repetitive behaviors, possibly through reducing lactate accumulation [64]. Metformin, commonly used for diabetes treatment, improves glycolysis and reduces astrocyte reactivity, thereby preventing apoptosis and enhancing synaptogenesis but also reducing astrocyte reactivity, preventing cell apoptosis, promoting synaptogenesis, enhancing neuroplasticity, and maintaining neuronal survival, showing significant therapeutic effects on ASD [65]. Another promising drug is ANAVEX2-73 (AV2-73), a mitochondrial-targeted antioxidant that has been shown to improve mitochondrial function and reduce oxidative stress in ASD [66]. AV2-73 works by targeting the mitochondrial electron transport chain, where it can neutralize ROS and protect mitochondrial DNA from damage [67]. In a preclinical study, AV2-73 was found to improve mitochondrial function and reduce oxidative stress in an animal model of ASD, leading to a significant improvement in behavioral symptoms [68]. Additionally, a brain-targeted H_2S donor cross-linked nanomicelle (Man-LA) has shown potential for ASD treatment. Man-LA improved symptoms in

ASD rats by promoting aerobic glycolysis and lactate production and prevented hippocampal neuronal damage [69]. These findings suggest that regulating lactate metabolism and restoring mitochondrial function will be effective strategies and research hotspots for future ASD treatment. This not only indicates new directions for drug research but also highlights the significance of exploring existing drugs with these effects in other diseases for ASD treatment, achieving the goal of repurposing old drugs.

7. Future research directions of lactate in ASD

The role of lactate in different pathological states still requires further investigation. Lactate can act as a promoter of neuroplasticity but may also trigger inflammation and neurotoxicity when accumulated excessively. Therefore, future clinical studies should focus on elucidating the specific mechanisms of lactate in various neurological diseases, particularly in ASD. ASD is characterized by impairments in social interaction, communication, and repetitive behaviors and is often associated with neuroinflammation and neurodevelopmental abnormalities. Given the role of lactate in neuroinflammation, neuroplasticity, and mitochondrial function, it is plausible that lactate-modulating therapies could offer significant benefits for ASD patients. Future clinical studies should not only explore the specific mechanisms of lactate in various diseases but also optimize lactate-modulating therapies to ensure their efficacy and safety in neuroprotection and repair.

Additionally, targeting lactate regulation therapy, in addition to pharmacological treatments, can also involve modulating specific enzymes, relevant transport proteins, and regulating glycolysis and associated metabolic pathways. For instance, targeting the PI3K/Akt/mTOR pathway, which is involved in regulating glycolysis, can reduce lactate production. Inhibitors such as rapamycin have been shown to affect this pathway and decrease glycolysis. Small molecules or gene therapies that specifically regulate lactate metabolism or histone lactylation could also provide more precise and effective treatment options. The use of advanced imaging techniques and biomarkers to monitor lactate levels and metabolic changes in the CNS could also enhance the diagnostic accuracy and therapeutic monitoring of neurological diseases [19].

In summary, research on the lactate mechanism provides new opportunities for the early diagnosis and precision treatment of neurological diseases. Future clinical studies may reveal more functions of lactate in the nervous system and offer innovative intervention strategies for the treatment of neurodegenerative diseases, neuroinflammation, and neurodevelopmental disorders. Future research should also elucidate the specific mechanisms of lactate in ASD and explore its potential as a biomarker and therapeutic target.

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