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Neuroinflammation in autism spectrum disorders: Exercise as a "pharmacological" tool

Chrystiane V.A. Toscano [a,1], Leonardo Barros [b,1], Ahlan B. Lima [c], Thiago Nunes [d], Humberto M. Carvalho [c], Joana M. Gaspar [d,e,*]

[a] Federal University of Alagoas, Maceió, AL, Brazil
[b] Department of Medicine, University of Alto Vale do Rio do Peixe (UNIARP), Brazil
[c] Department of Physical Education, School of Sports, Federal University of Santa Catarina, Florianópolis, SC, Brazil
[d] Department of Biochemistry, School of Biological Sciences, Federal University os Santa Catarina, SC, Brazil
[e] Laboratory of Bioenergetics and Oxidative Stress (LABOX), Department of Biochemistry, School of Biological Sciences, Federal University of Santa Catarina, Florianópolis, Brazil

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ABSTRACT

The worldwide prevalence of ASD is around 1%. Although the pathogenesis of ASD is not entirely understood, it is recognized that a combination of genetic, epigenetics, environmental factors and immune system dysfunction can play an essential role in its development. It has been suggested that autism results from the central nervous system derangements due to low-grade chronic inflammatory reactions associated with the immune system activation. ASD individuals have increased microglial activation, density, and increased proinflammatory cytokines in the several brain regions.

Autism has no available pharmacological treatments, however there are pedagogical and psychotherapeutic therapies, and pharmacological treatment, that help to control behavioral symptoms. Recent data indicate that exercise intervention programs may improve cognitive and behavioral symptoms in children with ASD. Exercise can also modify inflammatory profiles that will ameliorate associated metabolic disorders.

This review highlights the involvement of neuroinflammation in ASD and the beneficial effects of physical exercise on managing ASD symptoms and associated comorbidities.

1. Introduction

Autism spectrum disorder (ASD), popularly known as autism, is a neurodevelopmental condition that affects brain cortical and subcortical areas and result in an overgrowth of the brain in most 2.5-year-old ASD children (Courchesne et al., 2007; Schumann et al., 2010). However, the brain in ASD adults may be normal or decreased compared to children with ASD (Ha et al., 2015).

ASD diagnosis is completed according to the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5). Clinical signs emerge in childhood and persist into adulthood. ASD is characterized by deficits mainly in social communication and interaction, nonverbal communication, skills in developing, maintaining, and understanding relationships, and the presence of a restricted and/or repetitive pattern of behavior (Fig. 1) (American Psychiatric Association, 2014). A high prevalence of sensory symptoms has been documented, with reports ranging from 60 to 96 % of children with ASD exhibiting some degree of atypical responses to sensory stimuli (Baranek et al., 2013; Dunn et al., 2002). Sensory differences may contribute to many higher-order cognitive and social deficits associated with ASD [see review (Robertson and Baron-Cohen, 2017)]. Patients must have evidence of two of four subdomains of repetitive or restricted behaviors such as insistence on sameness, highly restricted or fixed interests, hypersensitivity or hyposensitivity, and stereotyped behavior (American Psychiatric Association, 2014).

In 2015 was estimated 52 million cases of ASD in the world, equivalent to a prevalence of one in 132 people (Baxter et al., 2015). Autism is more common in males than females, with a 3:1 ratio (Loomes et al., 2017). In the US, the prevalence of ASD is one in 54 children aged 8 years, with a 4.3 times higher prevalence among boys than girls

* Corresponding author: Department of Biochemistry, School of Biological Sciences, Federal University os Santa Catarina, SC, Brazil.
E-mail addresses: joanamgaspar@gmail.com, joana.gaspar@ufsc.br (J.M. Gaspar).
[1] Both authors equally contributed to the manuscript.

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(Maenner et al., 2020). The prevalence of ASD dramatically increased in the last years, caused by improved surveillance, diagnostic substitution, overdiagnosis, or an actual increase in prevalence (Chiarotti and Venerosi, 2020).

The exact etiology of ASD is still unknown. Currently, it has been recognized that a complex interplay and combination of genetic, environmental factors and immune dysfunction can play potential roles in its development (Fig. 1) (Lai et al., 2014; Muhle et al., 2004). Epigenetic mechanisms can be the prime molecular mediator in controlling how environmental factors interact with the underlying genetics to change brain development in ASD (Loke et al., 2015; Vogel Ciernia and LaSalle, 2016).

Genetic alterations associated with ASD may be a consequence of single-gene mutations or copy number variations (such as duplications, large deletions, inversions, and translocations of chromosomes) (Garcia-Forn et al., 2020). In particular, the perinatal environment has attracted much attention for its implications on brain development and functions. Environmental risk factors that affect ASD neurodevelopment and result in long-term alterations in brain physiology include neonatal hypoxia (Modabbernia et al., 2016), maternal obesity (Windham et al., 2019), valproate use during pregnancy (Christensen et al., 2013), maternal diabetes (Xiang et al., 2015), and advanced maternal and paternal age (Gao et al., 2020). Another important risk factor for ASD is the reduced levels of vitamin D in pregnant women and their infants and toddlers (Magnusson et al., 2016; Vinkhuyzen et al., 2018). Also, obese subjects have vitamin D deficiency (around 35 % higher than lean subjects) (Pereira-Santos et al., 2015), suggesting that both associated maternal obesity and vitamin D deficiency can increase the risk of offspring with ASD.

Children with ASD may be suffering from autoimmune disorders (Ormstad et al., 2018). Associated with the immune system activation, it has also been suggested that autism results from the central nervous system derangements due to chronic inflammatory reactions, with activation of microglial cells (Bjorklund et al., 2016; Vargas et al., 2005). Currently, there is no standard treatment for ASD. However, there are many ways to minimize the symptoms and maximize abilities (Eissa et al., 2018), with most ASD subjects responding better to highly structured and specialized programs. Understanding the molecular mechanisms of ASD to find therapeutic strategies that reduce the incidence and treat the core symptoms of ASD should be a central focus of future research (Eissa et al., 2018).

This mini-review focused on neuroinflammatory mechanisms involved in the biogenesis of autism spectrum disorders and a special attention was given to the exercise as a pharmacological tool for managing ASD symptoms.

2. Physiopathology of autism spectrum disorders

Autism results from alterations in the central nervous system's development, which change the brain's physiology and behavior. The physiopathology of autism remains unclear, but it likely involves several systems connectivity, neural, biochemical, neuroanatomical, cellular, and molecular features.

Brain areas involved in emotional control, social interactions, and motor coordination are compromised in subjects with ASD. Postmortem samples from ASD subjects show abnormalities in brain regions, particularly in the cerebellum, hippocampus, cortex, brainstem, and other subcortical areas.

Meta-analyses studies suggest consistent neuroanatomical changes both in grey-matter (such as the amygdala, hippocampus, and precuneus) and in white-matter structures (e.g., arcuate and uncinate fasciculi) (Bourgeron, 2015; Eissa et al., 2018; Mann et al., 2020; Mei et al., 2020; Varghese et al., 2017). The medial prefrontal cortex, superior temporal sulcus, temporoparietal junction, amygdala, and fusiform gyrus are hypoactive regions in autism across tasks in which social perception and cognition are used (Varghese et al., 2017). For executive dysfunction, frontal, parietal, and striatal circuitry are the main regions affected. These abnormalities may be associated with alterations in the maturation/migration of neurons in ASD patients. Postmortem studies have shown a reduction in neuronal number in the amygdala, fusiform gyrus, and cerebellum and have shown persistent neuroinflammation signs. Prefrontal cortical areas have increased markers of neuronal overgrowth and an increase in the neuronal dendritic spine in young children diagnosed with ASD compared to control brain tissue (Hutsler and Zhang, 2010). Replicating some of the neuropathological features seen in postmortem studies, a common finding in animal models of ASD is the altered density of dendritic spines (Varghese et al., 2017). The lateral nucleus of amygdala had reduced neuronal cells (Schumann and

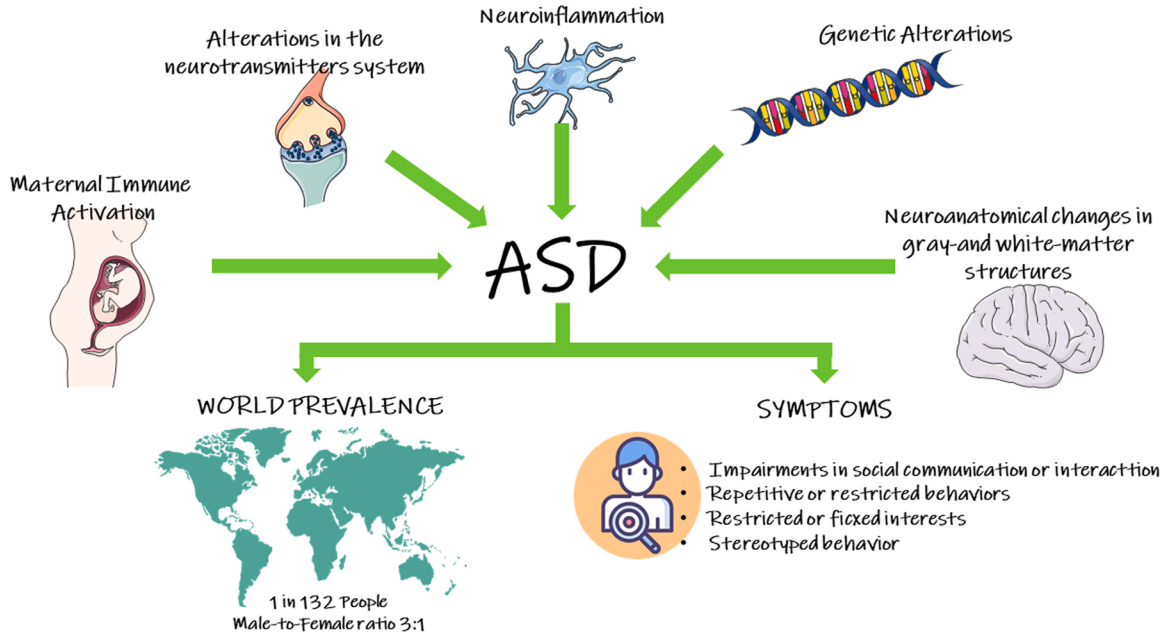

Fig. 1. Etiology and symptoms of autism spectrum disorders. The etiology and pathogenesis of ASD have not been completely identified. However, the combination of genetic and environmental factors and immune dysfunction can be underlying ASD development.

Amaral, 2006).

It has been documented, by electroencephalography, relevant differences in the timing of the response to auditory, visual, and tactile input in ASD subjects. Increased cortical representation of the visual periphery in ASD subjects was reported, suggesting early hyper-responsiveness (Frey et al., 2013). The neural responses to tactile stimulation are related to tactile hyper-responsiveness. In contrast, slightly later neural responses are related to tactile hypo-responsiveness and may involve higher-level processes such as attention, allocation, and assignment of emotional valence (Cascio et al., 2015). Using functional magnetic resonance imaging, different spatial activation patterns across cortical areas of the brain were observed as being responsible for these earlier and later sensory processing stages (Schauder and Bennetto, 2016).

Other modifications reported in ASD subjects include a significant increase in the neuropil in the frontal cortex and the anterior cingulate gyrus, reduced dendritic branching in the hippocampus, and decreased pyramidal neurons the inferior frontal cortex; reduced number and size of Purkinje cells in the cerebellum.

Regarding the brain immune cells, it was reported in ASD human samples an increase in microglial density in cortices (Morgan et al., 2010; Tetreault et al., 2012; Vargas et al., 2005); increase activated microglia in the striatum (Morgan et al., 2014), and no changes in the number of microglia in the amygdala (Morgan et al., 2014).

The genetic component is undoubtedly involved in the pathogenesis of ASD, with hundreds of genes linked to this pathology. However, each gene contributes to only a tiny percentage of the affected population. Recent large-scale genetic studies have highlighted hundreds of genes that have a role in synaptic function and development as risk factors for ASD pathogenesis (Bourgeron, 2015; Sanders et al., 2015).

Neuroligins (NLGNs) are well-characterized neuronal, post-synaptic, cellular adhesion molecules that mediate synaptic formation and function. NLGNs are composed of five family members in humans (NLGN1, 2, 3, 4X, and 4Y). Mutations in genes encoding NLGN3 and NLGN4 are associated with autism (Cast et al., 2021; Jamain et al., 2003; Kopp et al., 2020; Yan et al., 2005). More recently, a nonsense variant of NLGN2 in a human was associated with a neurobehavioral phenotype including anxiety, autism, hyperphagia, and obesity (Parente et al., 2017). Expression levels of NLGN2 influence the balance between excitatory and inhibitory neuronal signals, and dysregulation in this balance is associated with neurobehavioral disturbance, including autism (Bang and Owczarek, 2013; Rubenstein and Merzenich, 2003; Steffen et al., 2021). Alterations in several neurotransmitters are implicated in the development of ASD, including serotonin, dopamine, noradrenaline, GABA, and glutamate (Quaak et al., 2013). For instance, serotonin is involved in sleep, sensory perception, and appetite, which are often disrupted in ASD (Janusonis, 2014).

In summary, accumulated evidence converges in highlighting changes in the white and grey matter, blood-brain barrier disruption, abnormal synaptic overgrowth, and synapses density. All these mechanisms indicate a possible involvement of neuroinflammation in the development of ASD. A potential link between in utero or perinatal exposures to existing identifiable neuropathology may lie in the amount of inflammation that the brain is exposed during development.

3. Epigenetics in the etiology of ASD

The difficulty in understanding the etiology and pathophysiological mechanisms of ASD development arises from the complexity and highly interdependent interactions across body systems. Epigenetics is a mechanism that alters gene activity without changing the DNA sequence, leading to genomic modifications that are heritable during cell division (Waddington, 2011). Epigenetics is critical for the normal development and functioning of the human brain, representing an essential mechanism by which the environment can act on the genome leading to persistent changes in gene expression/ function. However, when epigenetics occurs improperly, they can induce significant adverse health and behavioral effects. Epigenetics modifications can influence and regulate gene activity both at the transcriptional and translational levels. The most characterized epigenetic changes are DNA methylation and post-translational modifications of histones (Vogel Ciernia and LaSalle, 2016). Epigenetic mechanisms generally result in the silencing or expression of genes, and therefore their occurrence during development can have a significant impact on the individual's behavior. Epigenetic alterations can affect the expression of neuronal proteins, hormonal receptors, and cytokines, and therefore have long-term consequences on the brain.

The maternal factors that influence epigenetic modifications include maternal stress, psychiatric disorders, chemicals, overnutrition, infection, and inflammation during pregnancy. These factors negatively impact brain development during fetal life and have been found to be associated with ASD development.

Maternal immune activation during prenatal development induces epigenetic alterations in the brain [DNA methylation (Basil et al., 2014), histone methylation (Connor et al., 2012), and miRNA expression (Hollins et al., 2014)], which is correlated with autism. For instance, microglia from the offspring of dams with allergic asthma displays hypermethylation of pro-inflammatory genes associated with autism (Vogel Ciernia et al., 2018). Maternal overnutrition during pregnancy modulates the epigenome in offspring and increases ASD susceptibility (Banik et al., 2017). Also, obesity as a chronic pro-inflammatory condition is a risk factor for developing neurologic diseases and altered behavior such as ASD (Zheng et al., 2017). It potentially might set a selective epigenetic program in offspring. However, the effect of maternal high-fat diet consumption during gestation and its role on epigenetics modulation of immunity for ASD development has not been completely identified yet.

Genome-wide alterations in DNA methylation in ASD brain samples have shown preliminary evidence to support the role of epigenetics in autism. DNA methylation in neurodevelopmental genes (such as PRRT1, TSPAN32, SPI1, IRF8, TNF-α, ITGB2, NRXN1, SH3, and SHANK3) encode proteins involved in the formation of synapses and the immune system. These are often changed in the dorsolateral prefrontal cortex, temporal cortex, cerebellum, and anterior cingulate gyrus of ASD subjects (Ladd-Acosta et al., 2014; Nardone et al., 2014, 2017). Also, methylated genes involved in microglial cell specification and synaptic pruning during brain development were the most affected (De Rubeis et al., 2014; Nardone et al., 2017). It was also detected in neurons of ASD subjects enriched CpGs regions for immune genes, such as TNF-α and the IFN-γ signaling innate immune response to viral infection protein OAS2 (Nardone et al., 2017). The offspring of the autoimmune ASD mice model showed hypermethylated DNA regions in several transcription factor motifs critical for early microglial development and immune activation, and the cytokines IL-6, IL4, IL-8, and Jak-STAT, TNF, and mTOR signaling (Vogel Ciernia et al., 2018).

Altogether, data support the hypothesis that environmental factors occurring in-utero, especially those with stress or inflammatory-related component, can alter epigenetic programming, in term of DNA methylation, contributing to neurodevelopmental and behavioral deficits in the offspring.

4. The role of maternal immune activation in the etiology of ASD

Multiple prenatal exposures, especially infection, have been linked to an increased risk of ASD in offspring. Perinatal brain development, especially during the first weeks of neonatal life, is particularly susceptible to abnormal immune activation consequences with detrimental consequences on brain development and, consequently, being important in the etiology of neuropsychiatric conditions such as ASD (Deverman and Patterson, 2009; Tsafaras et al., 2020) (Fig. 2).

Clinical and preclinical studies have suggested a link between maternal immune activation during pregnancy and the development of

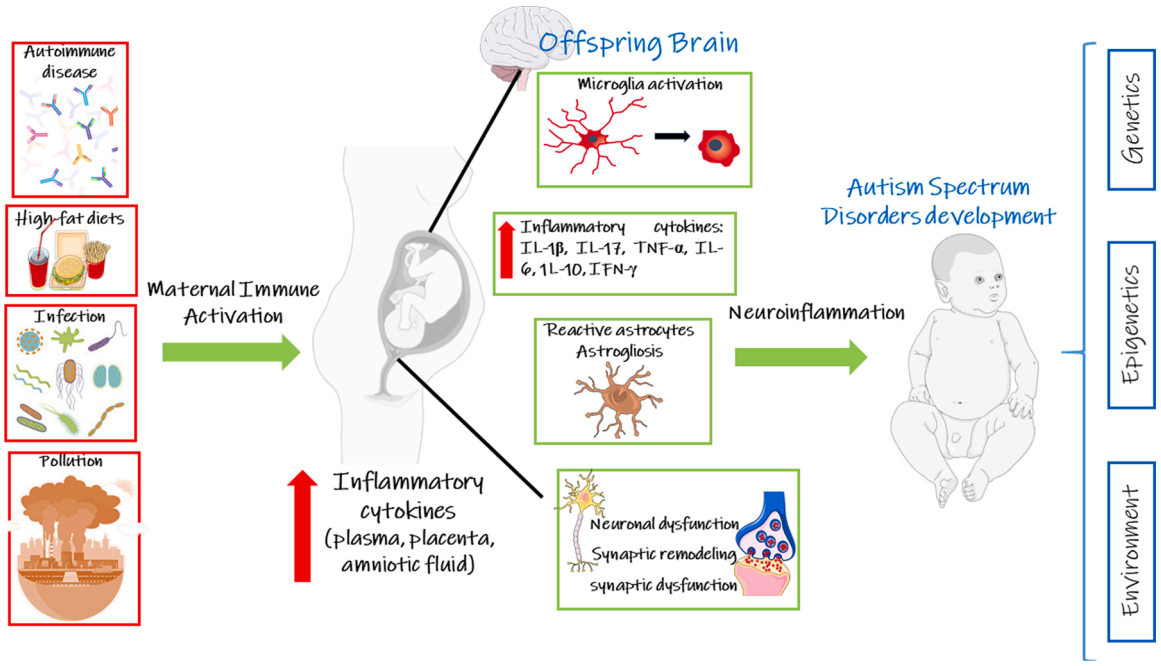

Fig. 2. Neuroinflammation associated with autism spectrum disorders. Maternal immune system activation is a risk factor that increases the chances of a child develops ASD. The increased inflammatory cytokines and autoantibodies that react to fetal brain tissue may change proper synaptic development in the offspring and that are linked to behavioral abnormalities seen in ASD, including repetitive behaviors, stereotypies, anxiety, and impaired social behaviors.

autism spectrum disorders (Atladóttir et al., 2009, 2010; Brown et al., 2014; Choi et al., 2016; Lee et al., 2015; Rudolph et al., 2018). An emerging human diagnostic marker for ASD is detecting increased IL-6 concentrations in the umbilical cord plasma and elevations in several other cytokines (Madsen-Bouterse et al., 2010).

It was observed a positive association between maternal autoimmunity and ASD development (Atladóttir et al., 2009). This relationship can be attributable to a combination of a common genetic background but also a possible prenatal antibody exposure or alteration in the fetal environment during pregnancy (Atladóttir et al., 2009) that could cross the placenta and alter fetal brain development (Braunschweig et al., 2012; Dalton et al., 2003; Zimmerman et al., 2007).

Severe bacterial or viral infections in pregnancy are similarly associated with an increased risk of ASD in children (Atladóttir et al., 2010). Increasing maternal levels of C-reactive protein were significantly associated with autism in offspring, suggesting that maternal inflammation may significantly impact ASD development (Brown et al., 2014). Increase concentrations of IFN-γ, IL-4, and IL-5 in the maternal serum of during midgestation were significantly associated with a 50 % increased risk of ASD (Goines et al., 2011). Increasing the plasma level of cytokines in the mother can cross the placental and blood-brain barrier to trigger cytokine expression in the brain.

In preclinical studies with rodent models, it has been observed that prenatal lipopolysaccharide (LPS) injections induce activation of the immune system with alterations in synaptic plasticity, white matter development, and in social, cognitive, and motor behaviors of offspring (Choi et al., 2016; Fernández de Cossío et al., 2017; Foley et al., 2015; Urakubo et al., 2001). In detail, LPS injection in E16 pregnancy rats induces an increase in IL-1β, IL-6, and TNF-α in the placenta and amniotic fluid. An increase in TNF-α was also observed in the fetal brain (Urakubo et al., 2001). Maternal immune activation induced by LPS injection in E17 mice induces an increased number of pyramidal and granular cells in the hippocampus, as well as the shrinkage of pyramidal cells, impaired distinct forms of learning and memory, but not motor function or exploration in the adult offspring (Golan et al., 2005). Specifically, IL-17 seems to have an essential role in maternal immune activation for ASD development in offspring. T helper 17 (TH17) cells and the effector cytokine IL-17a are required in mothers for maternal immune activation-induced abnormal cortical phenotype and behavioral abnormalities in offspring (Choi et al., 2016).

Maternal nutrition directly affects offspring's health. There is a significant vitamin D deficiency in pregnant women and their infants and toddlers, and it is associated with the current increase in ASD. Vitamin D has anti-inflammatory effects, reducing the risk and severity of inflammatory cytokines in the brain. The lowest vitamin D levels during the first trimester of pregnancy were associated with a fourfold risk of ASD in the offspring (Chen et al., 2016; Vinkhuyzen et al., 2018). Calcitriol (Vitamin D) has anti-autoimmune effects, increases T-regulatory cells, protects neural mitochondria, and can be used to alleviate neuroinflammation (Huang et al., 2015). Obesity is also a risk factor for vitamin D deficiency.

Obesity is considered a low-grade chronic inflammatory disease. Rates of maternal obesity have risen due to more significant numbers of obese pregnant women and excess weight gain during pregnancy. Maternal obesity influences the health of both the mother and child. A clear association between maternal obesity and cognitive function, mental health, and increased risk of autism spectrum disorder in the offspring may be influenced by additional biological or social factors (Contu and Hawkes, 2017; Hatanaka et al., 2017). Large cohort studies from Canada, the US, and the UK observed that children born to obese mothers were more likely to be diagnosed with autism (Bilder et al., 2013; Dodds et al., 2011; Krakowiak et al., 2012). High-fat diet-fed dams generate offspring with increased anxiety- and depression-related behaviors and decreased cognitive functions, correlated with microglial activation and increased expression of proinflammatory cytokines in the amygdala and hippocampus (Bilbo and Tsang, 2010). Maternal high-fat feeding consumption leads to perturbations in serotonergic and dopaminergic systems in the offspring. High-fat diet consumption decreases the proliferation of neuronal progenitor cells, synaptic stability, and reduces the length and branching of dendrites in animal offspring born to obese mothers (Hatanaka et al., 2017). The increase in inflammatory cytokines, leptin, and insulin in obese mothers severely influence fetal brain development (Estes and McAllister, 2015; Rivera et al., 2015). The effect of gestational programming by high-fat diet consumption sets a

pro-inflammatory profile is partially dependent on an epigenetic program of immunity, promoting brain structural abnormalities in the offspring.

In conclusion, acute or chronic maternal immune activation alters proinflammatory cytokine levels in the fetal environment, impacting neuroinflammation mechanisms, developing brain, and consequently ASD development.

5. Neuroinflammation in neurodevelopment disorders

The complexity and high interactions across body systems during the course and development of ASD make it difficult to clarify this disorder's etiology. However, several studies hypothesized that chronic inflammation and neuroinflammation during early brain development could cause behavioral and cognitive impairments, impacting the etiological pathway of ASD (Ashwood et al., 2011; Liao et al., 2020; Sciara et al., 2020) (Fig. 2).

Inflammation and dysregulation of the immune system are clinical features of ASD (Ashwood et al., 2011; Ashwood and Wakefield, 2006). Elevated plasma levels of pro-inflammatory cytokines such as IL-1β, IL-6, IL-17, IL-12p40, and TNF-α were found in 3 to 9-year-old children with ASD (Inga Jácome et al., 2016b). The plasma cytokine levels were also correlated with the severity of ASD symptoms, meaning that increasing cytokine levels were associated with more impaired communication and aberrant behaviors (Ashwood et al., 2011; Inga Jácome et al., 2016a). Peripheral inflammatory markers can also predict comorbidities in autism, as well as reinforce and aid informed decision-making in ASD (Inga Jácome et al., 2016a), highlighting the role of chronic inflammation in ASD etiology.

The inflammatory process associated with ASD is extended to the central nervous system as neuroinflammation. Neuroinflammation is a well-orchestrated inflammatory response within the brain or spinal cord, mediated by various groups of glial cells, particularly astrocytes and microglia. The inflammatory mediators, namely cytokines, chemokines, reactive oxygen species, and secondary messengers, are mainly produced by microglia, astrocytes, and peripherally derived immune cells (DiSabato et al., 2016). Astrocytes and microglia act in concert as a surveillance system in the central nervous system, ensuring efficiency of the inflammatory processes against pathogens without disrupting homeostasis under physiological conditions. Astrocytes are the most abundant cells in the central nervous system, with essential roles in support neuronal function, transport of substances across the blood-brain barrier, energy storage, regulation of neurotransmission, and the immune regulation of the brain. Astrocytes can maintain brain homeostasis in response to metabolic alterations by sensing nutrients, hormones, and other metabolites (Meldolesi, 2020). Microglial cells contribute to immune surveillance in the central nervous system. Microglia can acquire various phenotypes that determine the consequences of the inflammation, controlling the balance between promotion and suppression in neuroinflammation. Microglia are responsible for regulating the majority of cytokine levels in extracellular areas of neighboring neurons and astrocytes (Eroglu and Barres, 2010). Both microglia and astrocytes modify their morphology to rapidly adapt to brain changes, influencing each other with a series of stimulatory signals, such as cytokines, and ATP, to initiate an immune response (DiSabato et al., 2016). As a disturbing process occurring at early brain development stages, chronic neuroinflammation can be involved in the biogenesis of behavioral and cognitive impairments. Neuroinflammation plays a role in developing and maintaining the dendritic spines in glutamatergic and GABAergic neurotransmission (Alabdali et al., 2014; El-Ansary and Al-Ayadhi, 2014). Cytokines can impact the length, location, and organization of dendritic spines on excitatory and inhibitory neurons and recruit and impact glial cell function around the neurons (Eroglu and Barres, 2010), with consequences on the development that may ultimately contribute to the ASD behavioral and cognitive symptoms.

ASD children had increased numbers of circulating monocytes, essential precursors for macrophages, dendritic, and microglial cell activation (Rodriguez and Kern, 2011; Sweeten et al., 2003). Additionally, evidence of immune system activation, including an abnormal CD4: CD8 T cell ratio, a high number of DR+ (activated) T cells, high urinary neopterin levels, and increased cytokine production, has been reported in autistic children (Sweeten et al., 2003). Immunoreactivity of astrocytes was detected in brain regions of ASD subjects. A significant increase in GFAP was observed in the postmortem superior frontal cortex, parietal cortex, prefrontal cortex, and cerebellum (Edmonson et al., 2014; Laurence and Fatemi, 2005). GFAP levels are also increased in fresh-frozen brain tissue of the cerebellum, middle frontal gyrus, and anterior cingulate gyrus from ASD subjects (Vargas et al., 2005).

Samples from cerebrospinal fluid, blood, and postmortem brain tissue from ASD patients have shown an imbalance in the immune cell with changes in response patterns, the presence of autoantibodies, increased levels of proinflammatory cytokines (Businaro et al., 2016; Masi et al., 2015; Nadeem et al., 2019), decreased levels of anti-inflammatory cytokines, and activation of microglia with changes in the microglia-neuronal spatial organization (Lee et al., 2017; Morgan et al., 2010; Rodriguez and Kern, 2011).

Increased densities of microglia were observed in the frontoinsular and visual cortex of the autopsy brains of ASD patients comparing to control brains, using an optical fractionator probe (Tetreault et al., 2012). In ASD subjects, utilizing the microglia marker IBA-1 through optical fractionator was observed an increase in microglia density in the brain sections of the dorsolateral prefrontal cortex, with markedly morphological alterations of microglia including enlargement of soma, retraction, and thickening of processes, and extension of filopodia (Morgan et al., 2010). This study also shows an increase in microglial cell density in the gray-matter and an increased somal volume of microglia in the white-matter of ASD subjects (Morgan et al., 2010). Amygdala also shows strong signs of excessive microglia activation; however, an evident heterogeneity activation profile within the ASD cohort was detected (Morgan et al., 2014).

Changes in microglia density can be accompanied by changes in microglia phenotype and morphology, which correlate with specific functions and indicate the brain's pathophysiological state. Six structurally and functionally microglial phenotypes were quantified using an unbiased stereological approach in the postmortem human temporal cortex (immuno-stained with Iba1) of ASD subjects, showing a decreased density of ramified microglia. However, an increased density of primed microglia in ASD subjects compared with controls, whereas no group difference in the total density of all microglial phenotypes was found (Lee et al., 2017). Positron emission tomography and a radiotracer for microglia were used to identify brain regions associated with excessively activated microglia and distribution patterns in the whole brain of men diagnosed with ASD (Suzuki et al., 2013). The authors identify increased microglia activity in the cerebellum, fusiform gyri, and the anterior cingulate and orbitofrontal cortices (Suzuki et al., 2013).

The characterization of the activation profile of microglia in the brain tissue and cerebrospinal fluid was evaluated in ASD subjects (Vargas et al., 2005). An active neuroinflammatory process was observed, with marked activation of microglia and astroglia, in the cerebral cortex, white matter, and in the cerebellum of autistic patients; the cerebrospinal fluid has a significant increase in proinflammatory cytokine MCP-1 (Vargas et al., 2005). Considering the hypothesis that chronic neuroinflammation during early brain development can cause behavioral and cognitive impairments, these alterations are thought to be relevant to synaptic dysfunctions in autism.

Microglial-specific markers TREM2, DAP12, and CX3CR1, were detected with a higher expression in the prefrontal cortex of autistic people compared to matched controls. The expression of TREM2 was the highest of all microglial markers in brain tissue from ASD patients (Edmonson et al., 2014). However, in the postmortem cerebellum, the

expression of microglial markers TREM2, DAP12, CX3CR1, and AIF1 was lower in autism tissue than in control tissue (Edmonson et al., 2014).

Corroborating the neuroinflammatory profile of microglia activation in postmortem brain of ASD subjects is the higher levels of proinflammatory cytokines (such as IL-1β, IL-6, IL-8, INF-γ, and TNF-α) detected in both brain specimens and blood of autistic patients compared with controls (Li et al., 2009; Vargas et al., 2005; Wei et al., 2011). The middle frontal gyrus of ASD patients showed an increase TGF- β1, increased MCP-1, IL-6, and IL-10 in the anterior cingulate gyrus, and only MCP-1 was increased in CSF (Vargas et al., 2005). However, in the dorsolateral prefrontal cortex of ASD subjects, there are no changes in characteristic markers of microglial activation, such as IL-6, IL-1 β, and TNF- α (Chana et al., 2015). Elevated levels of TNF-α are associated with disrupted pineal melatonin release and sleep dysfunction in ASD (da Silveira Cruz-Machado et al., 2021). It is proposed that circadian dysregulation in ASD is intimately linked to amplified immune-inflammatory activity, leading to sleep disturbances, as well as cognitive and behavioral alterations (da Silveira Cruz-Machado et al., 2021).

IL-6, a proinflammatory cytokine, was increased in the frontal cortex (Li et al., 2009) and the cerebellum (Wei et al., 2011). It was also reported significant increases in Th1 cytokine (IFN-γ), but not in Th2 cytokines (IL-4, IL-5, and IL-10) in brain tissues of ASD, which indicates that ASD brain can have an excess of adaptive response through activation of the Th1 pathway rather than activation of the Th2 pathway (Li et al., 2009).

In a mouse model of autism, the increased levels of IL-6 were associated with neuro-anatomical abnormalities (Wei et al., 2012a, b). Both excitatory and inhibitory synapse formation and transmission are changed by increased levels of IL-6, as well as the shape, length, and distribution pattern of dendritic spines (Wei et al., 2012a). These observations suggest that innate neuroimmune reactions may play a pathogenic role in ASD.

Altogether, these studies demonstrate abnormal microglial-specific gene expression in autistic brains, indicating that microglial activation patterns may play a pathogenic role in ASD development. Future therapies might involve drugs that modify neuroglial responses in the brain. While the precise influence of peripheral cytokines on the central nervous system immune environment in ASD has yet to be elucidated, neuroimmune alterations can be responsible for the phenotypic heterogeneity and severity observed in patients with autism. Indeed, many of the ASD features seem to have different severity levels also depending on changes in immune responses, confirming the intimate bond between neurodevelopment and immune processes

6. Benefits of exercise in ASD

Physical exercise is a non-pharmacological intervention with well-documented beneficial effects both in healthy people and in people with metabolic and neuropsychiatry disorders, such as depression, anxiety, schizophrenia, dementia, and other neurodegenerative diseases (Chen et al., 2020; Zhao and Jiang, 2020). Currently, no drugs are available to cure autism. However, ASD treatment requires integrated approaches, such as pedagogical and psychotherapeutic interventions and pharmacological treatment, to control specific behavioral symptoms, such as self- and hetero-aggression, hyperactivity, stereotyped behavior, and insomnia.

From the 1970s, the first studies related to the positive effects of the intervention with physical exercise, as an adjunct treatment, for the population with ASD (Fig. 3) (Best and Jones, 1974). Systematic reviews and meta-analysis studies have shown the existence of a positive relationship between physical exercise and the reduction of stereotypical behavior (Petrus et al., 2008; Toscano et al., 2018a), as well as, reduction deficits in social interaction (Bremer et al., 2016) in ASD subjects. However, in some studies the description of the exercise interventions models for the ASD population are still not clear in specific details such intensity, volume and frequency of exercise (Bremer et al., 2016; Lang et al., 2010; Sowa and Meulenbroek, 2012), as well as in the diagnostic category of ASD (Fragala-Pinkham et al., 2008, 2011; Hinckson et al., 2013). Besides the beneficial effect of exercise in ASD, there are no specific recommendations for the characteristics of the exercise intervention programs as well as procedures to motivate the adherence and participation of ASD subjects in physical exercise programs.

Studies have proposed that limited levels of physical activity, motor skills and fitness, particularly in children and adolescents with ASD, may accentuate social and emotional deficits and the associated comorbidities (Bandini et al., 2013; Batey et al., 2014; Bremer et al., 2016; Curtin et al., 2014; Tyler and MacDonald, 2014). More specifically, children with poor motor coordination spent significantly less time doing moderate to vigorous physical activity (measured over seven days using accelerometry), and physical exercise reduces physical motor deficits in children with developmental coordination disorder (Batey et al., 2014). Exercise improves psychopathological profile and cognitive function, and also decrease of behavioral stereotypy (by recording the frequency of predetermined child-specific stereotypic behaviors from baseline recordings) and aggressive behaviors (Bremer et al., 2016; Oriel et al., 2011; Tan et al., 2016).

Intervention studies with aerobic physical exercises, aquatic and terrestrial, have shown a reduction in stereotyped behaviors (Bahrami et al., 2016; Celiberti et al., 1997; Kern et al., 1984, 1982; Levinson and

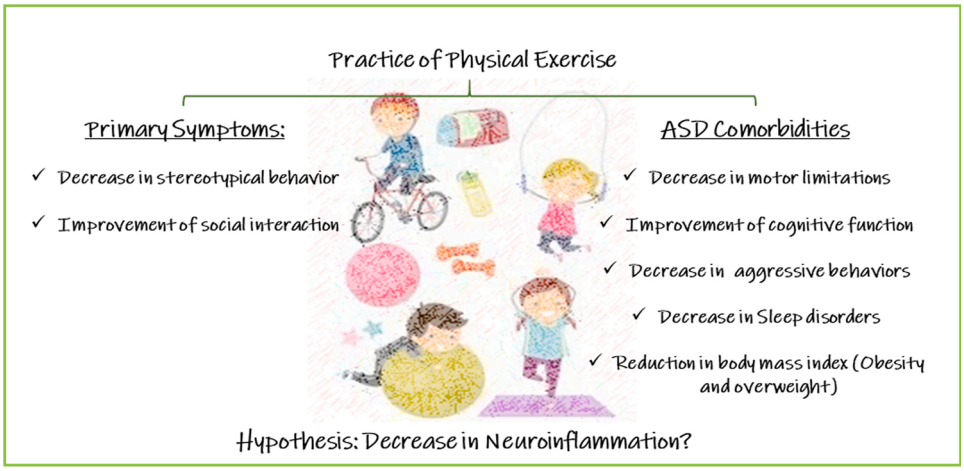

Fig. 3. Benefits of exercise in autism spectrum disorders. Physical exercise intervention has a positive effect both in primary symptoms of ASD as well as in comorbidities.

Reid, 1993; Liu et al., 2016; Rosenthal-Malek and Mitchell, 1997; Watters and Watters, 1980). In a controlled trial to assess the impact of exercise on stereotypic behaviors, Bahrami et al. (2012) found significant reductions in stereotypic behavior (using the Gilliam Autism Rating Scale – 2nd ed.) following martial arts intervention (60 min session, four days/week during 14 weeks) (Bahrami et al., 2016). Similarly, a significant reduction in stereotypic behavior (using Aberrant Behaviour Checklist – Community) was observed with horseback riding intervention (60 min session/week/ 10 consecutive weeks) (Gabriels et al., 2012). Both studies reported an effect size of 0.9. Intervention studies using jogging (1–5 sessions/week, 20 min/session for a total of 10 sessions) significantly reduces stereotypic behaviors (measured by the frequency of child-specific behaviors, such as body rocking, biting self, hand flapping, etc.), with an effect size of 3.0 (Rosenthal-Malek and Mitchell, 1997). Physical exercise intervention programs based on coordination and strength exercises (40 min/session, two sessions/week for 40 weeks) showed a decrease in the accumulated number of item for social interaction, attention deficit, reactivity, verbal stereotypes, motor stereotypes, and sleep disturbances in children and adolescents with ASD (accessed by the Autistic Traits Assessment Scale) (unpublished results).

It appears to exist an association between the reduction of primary behavioral symptoms and improvements in the academic responses, observed by the increase in the frequency of correct academic answers given and a significant increase in the number of work tasks performed (Kern et al., 1984; Rosenthal-Malek and Mitchell, 1997). Interventions with 15-min jogging increased about 7.5 % the time spent engaged in academic tasks (Nicholson et al., 2011; Oriel et al., 2011). These results can be explained by the improvements in attention (especially in the dorsolateral prefrontal cortex) and changes in neurotransmitters' concentration (Zhang et al., 2020). It was observed that physical activity (horseback riding) significantly improves social responsiveness and social interactions, measured by parent-reports (Bass et al., 2009; Ward et al., 2013). Also, horseback riding intervention significantly improves adaptive behavior (evaluated by Vineland Adaptive Behaviour Scales – Interview Edition, Survey Form), including communication, social, and daily living skills (Gabriels et al., 2012). Long-term Kata techniques training (1 session/day, four days/week for 14 weeks) also has beneficial effects in social dysfunction of children with ASD, accessed by the Gilliam Autism Rating Scale, with a large effect size of 1.4 (Movahedi et al., 2013). Similar reductions in behavioral symptoms were observed using yoga and dance interventions (8 sessions 45 min/session), accessed by Behavioural Assessment System for Children (Rosenblatt et al., 2011). Recently, it has been shown that a mini-basketball training program (40 min/session, five sessions/ week) for 12 consecutive weeks had an improvement in social communication (lower scores, assessed by Childhood Autism Rating Scale) in children with ASD (Cai and Yu, 2020). This study shows that white matter integrity of the exercise group showed higher fractional anisotropy in the body of corpus callosum, fornix, right cerebral peduncle, left posterior limb of the internal capsule, left anterior corona radiate and left superior fronto-occipital fasciculus (Cai and Yu, 2020).

The impact of exercise intensity is not well understood in the literature (Bremer et al., 2016). In a systematic review with meta-analysis, identified that an average frequency of three times per week, with the duration per session that could vary from 15 to 90 min per session and exercise programs ranging from 8 to 48 weeks had positive effects in ASD symptomatology (Ferreira et al., 2019). An intervention study with a small group of children with ASD showed that interventions with short 10-minute sessions, light to moderate intensity, induce better responses in reducing stereotyped behaviors than more prolonged and intense sessions (Schmitz Olin et al., 2017).

Sleep disorders occur in 44–83 % of these children with ASD (Shui et al., 2018). Studies have shown that ASD children with better physical activity levels have less difficulty falling asleep and fewer sleep disorder patterns, improving the overall sleep quality, reported by parents and by completing the Children's Sleep Habits Questionnaire (Wachob and Lorenzi, 2015).

Obesity has a high prevalence in children and adolescence with ASD, mainly caused by sedentary behavior resulting from the symptomatology profile, developmental coordination disorders, sleep disorders, and the continuous use of psychotropic medications (Bandini et al., 2013; Curtin et al., 2014; Tyler and MacDonald, 2014). Both obesity and neuropsychiatric disorders are characterized by low-grade systemic inflammation and neuroinflammation in several brain regions (Martins et al., 2019). Persistent low-grade inflammation interferes with the regulation and consequent function of neurotransmitters related to emotions (Barha et al., 2017; Hodes et al., 2014). Physical exercise reduces body mass, with improvements in obesity, in children with ASD. Participants of the intervention studies using a treadmill walking program for 36 weeks, 15−20 min, three days a week, moderate level, had a significant increase in exercise capacity and monthly caloric expenditure coupled with a decrease in body mass index (Pitetti et al., 2007). ASD individuals that endorsed in an intervention study playing an active video game for six weeks, 30 min on four days a week, have a reduced body mass and body mass index, with minimal changes to waist-to-hip ratios, triceps skinfolds, and stress and anxiety (Strahan and Elder, 2015). Physical activity program based on coordination and strength exercises for 48 weeks, 30-minutes on two days a week with moderate level showed improvements in the metabolic profile (high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and total cholesterol). However, no changes in body mass in children with ASD were observed (Toscano et al., 2018b).

Although the molecular mechanisms involved in the beneficial effects of exercise remains unknown, we could hypothesize that exercise improvements in body mass and in whole-body metabolism could also improve inflammatory profile and neuroinflammation in ASD children leading to the amelioration of the symptomatology.

On the other hand, obese individuals have a higher risk for developing neuropsychiatric disorders such as depression. Depression is four times more prevalent in the ASD population. The impairments associated with depression may be compounded by additional psychiatric comorbidities, such as anxiety, which is also highly prevalent in individuals with ASD (Hudson et al., 2019). Similar to ASD, depression is associated with increased immune system activity, increased leukocyte function, and the release of pro-inflammatory cytokines (IL-1, IL-2, IL-6, and TNF-α) (Colasanto et al., 2020; Liu et al., 2020). It is widely accepted that exercise effectively treats mild to moderate depression comparable to mains antidepressant medication and cognitive behavioral therapy (for review, see (Bueno-Antequera and Munguía-Izquierdo, 2020). Exercise-induced reduction in peripheral inflammation and neuroinflammation is linked to better performance of neurotransmission and brain plasticity.

As reviewed throughout this manuscript, inflammation and neuroinflammation are relevant biological factors that interact with genetic, external stimuli, and neurophysiological mechanisms and can contribute to ASD development and symptoms. Physical exercise stimulates several organs to secrete cytokines or metabolic hormones that act all body, including on the brain having pro-cognitive functions. The exercise-stimulated cytokine release has essential roles in modulating neuronal metabolism, neuroinflammation, and neuroplasticity underlying brain function changes (Bay and Pedersen, 2020; Murphy et al., 2020). It is well accepted that physical exercise has beneficial effects for the management of several psychiatric disorders, promoting molecular changes that induce an anti-inflammatory state over a chronic pro-inflammatory condition in the periphery and central nervous system (Ignácio et al., 2019). We could hypothesize that the beneficial effects of physical exercise over ASD symptomatology and comorbidities could be trigger by a decrease in the neuroinflammatory profile.

In summary, literature recognizes a wide range of benefits of exercise intervention programs in the symptomatology in the ASD population. However, the molecular and cellular mechanisms induced by exercise

interventions need to be explored and investigated. The available data are limited by small sample size and large variability in the frequency of intervention sessions (Bremer et al., 2016; Ferreira et al., 2019; Sowa and Meulenbroek, 2012; Tan et al., 2016). Additional research is necessary to better understand which specific physical exercise interventions are more appropriate for the population with ASD, considering the variability in the intensity of disorder's symptomatology. It is recommended that specific exercise intervention protocols should considered procedures to motivate the adherence and participation of children and adolescents with ASD in physical exercise programs.

6.1. Environmental enrichment

Physical exercise can have similar beneficial effects as enriched environments on brain and behavior in humans and other animals (for review, see (Hillman et al., 2008)). Environmental enrichment is a combination of complex inanimate and social stimulation to reduce stereotypical behavior by counteracting boredom and engaging specific actions. Environmental enrichment involves increasing novelty and complexity in environmental conditions to enhance sensory, cognitive, and motor stimulation. One way to attempt one of the components of environmental enrichment has been to provide animals with ad libitum access to running wheels or treadmills to assess the effects of increased physical activity alone. For humans, sensory integration is a preferred term for "environmental enrichment", involves different types of sensory and motor exercises on a daily basis. In humans, enriching the children's environments is an attempt to increase social interactions and cognition, promoting learning in a guided participation context (Ball et al., 2019).

In children, enriched physical education (specifically tailored physical activity games) provide a unique form of enrichment that impacts children's cognitive development through motor coordination improvement, improving children's physical activity habits later in life (Pesce et al., 2016). Using animals, a comparison of enrichment, running, and a combination of enrichment and running revealed that only mice with access to running had increases in neurogenesis, neural number and survival, and neurotrophin levels (Kobilo et al., 2011).

In neurodevelopment disorders, environmental enrichment and increased voluntary physical exercise have generally been associated with sensory integration therapy and positively influence the symptoms of the neurological disorders (Nithianantharajah and Hannan, 2006). The positive effects of environmental enrichment and increased voluntary physical exercise are mediated by a decrease in neuroinflammation and gliosis, enhanced neurogenesis, and cellular plasticity in specific brain regions, including the cerebral cortex (Nithianantharajah and Hannan, 2006).

In neurodevelopment disorders, such as ASD, it is believed that environmental enrichment can compensate for the deprivation of sensory/social/motor inputs caused by dysfunctional sensory systems (Ball et al., 2019). Rett syndrome is an autistic spectrum developmental disorder associated with mutations in the X-linked Mecp2 gene and severe behavioral and neuropathological deficits. In a genetic animal model of Rett syndrome ($MeCP2^{tm1Tam}$ mice), environmental enrichment and running wheel exercise reverses the effect of MeCP2 deficit affective phenotype, normalized the hedonic response, and ameliorates motor coordination, by partial normalization of HPA axis function (by rescued basal serum corticosterone), and by an increase in the hippocampal BDNF protein levels (Kondo et al., 2008, 2016). Environmental enrichment also reduced ventricular volumes, which correlated with improved locomotor activity (Nag et al., 2009).

In an animal model of ASD (valproic acid exposed rats), physical exercise, multisensory stimulation, and enriched housing were associated with improved anxiety-like behavior, social and cognitive deficits as well as reduced repetitive/stereotypic behavior. In another animal model of ASD, the BTBR T + Itpr3tf/J (BTBR) mice, environmental enrichment improves systemic metabolism, learning/memory, anxious behavior, increased social affiliation, and locomotor activity (Queen et al., 2020). In a genetic mouse model of ASD (NL3R451C), environmental enrichment reduces body weight and increased social phenotype; however, it decreases locomotor activity and increased aggression behavior (Burrows et al., 2020).

Environmental enrichment resulted in increased neurogenesis, neuronal activity, increased dendritic spine density, increase brain-derived neurotrophic factor (BDNF), which is a protein that promotes neuron growth and maturation (Bechard et al., 2016; Queen et al., 2020; Schneider et al., 2006; Yamaguchi et al., 2017). Sensory integration techniques are commonly used to treat symptoms of ASD, and other developmental disorders, to improve dysfunctional sensory processing (Aronoff et al., 2016; Woo et al., 2015). Sensory integration using fine and gross motor activity is especially effective in reducing hyperactivity and attentional deficit in school-age children when combined with executive functioning therapy (Salami et al., 2017). Benefits of increased activity have been shown without the other aspects of enriched environments in children with neurodevelopment disorders. Still, at least one study (Salami et al., 2017) suggests that combination therapy, environmental enrichment, plus physical exercise is most beneficial.

7. Conclusion

In summary, the etiology of ASD is associated with increased immune system activity, astrogliosis, microglial activation, and the release of proinflammatory cytokines (IL-1, IL-2, IL-6, and TNF-α) in the brain. The detailed effects of cytokines on neural immune environment in ASD has yet to be elucidated, however these changes can be responsible for the phenotypic heterogeneity and severity observed in patients with autism. Indeed, many of the ASD features seem to have different severity levels also depending on changes in immune responses, confirming the intimate bond between neurodevelopment and immune processes

Regular physical exercise has several health benefits and is a cost-effective strategy for the promotion of brain health. Specifically, physical exercise had important improvements in the symptomatology dyad of ASD subjects. However, the exact neurobiological mechanisms involved in the therapeutic response to physical exercise have not yet been clarified. Based on preclinical and clinical studies in patients with other psychiatric disorders, we could hypothesize that exercise can reduce the inflammatory profile and neuroinflammation in ASD subjects leading to the amelioration of the symptomatology.

In conclusion, the essential benefits of exercise for ASD symptoms highlight exercise programs as a powerful complementary therapy to minimize symptoms among ASD subjects. Using exercise activities improves motor performance and may indirectly affect the core social communication impairments of individuals with ASDs by providing greater opportunities for socialization with peers and better attentional focus. We strongly recommend that structured and personalized exercise programs (combining components of aerobic, resistance, flexibility, and neuromuscular training) should be included within the care plan for individuals with ASD, given the multisystem and systemic effects in the ASD of exercise interventions.

Authors' contributions

All authors revised and edited the manuscript, approved the final version to be submitted, and take responsibility for the manuscript's integrity and accuracy.

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