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The neuroinflammation origin of autism spectrum disorder (ASD) – the literature review

Michalina Pytka[1], Weronika Dalmata[1], Paulina Należna[1]

[1] Student's Scientific Club of Department of Applied Psychology, Medical University of Lublin, Chodźki 7 street, 20-093 Lublin, Lubelskie Region, Poland; michalinapytka@gmail.com

Abstract

Introduction and state of the knowledge: The origin of neuroinflammation in autism spectrum disorder (ASD) remains unknown. The presence of immunological dysregulation in ASD is observed as abnormalities in lymphocytes subpopulations and alterations in pro-inflammatory cytokines' levels. Also kynurenine and histaminergic pathways are dysregulated, causing additional changes in the brain's structure and physiology. Inflammatory status include intestines as well the gut microbiota present characteristic features in ASD.

Materials and methods: The literature search was done using PubMed database up, focusing on the newest knowledge concerning ASD.

Aim: The aim of this review is to summarise the newest knowledge about molecular basis of neuroinflammation in ASD, to distinguish target molecules, that can predict autism's onset and to find dietary solutions, that can alleviate autistic behavioral features by tackling histaminergic and tryptophan pathways.

Conclusion: Concerning chronic inflammatory state's presence in ASD, exact target molecules' levels can be checked in order to proove changes in immune system. To allieviate symptoms such as social cognition, meditherian diet, probiotics, magnesium, B vitamins and physical excercises are highly recommended.

Key words: ASD; gut microbiota; tryptophan; kynureine; histaminergic pathway;

Introduction

ASD is a group of neurodevelopmental disorders that becomes more prevalent – especially in developed countries [1]. Impairments in social functioning are the most popular features that people are aware of. Recent research shows an alterations in cytokines' levels, which leads to the concept of inflammation in ASD, which causes brain's structural changes via gut microbiota [2-3].

It is estimated that one in 70 boys and one in 310 girls are estimated to suffer from ASD (5). However, Loomes R et al claim that the number of men to the number of women is 3:1. It is generally believed that it is 4:1, so as a consequence of this girls who fit the ASD criteria are more likely to not get a professional diagnosis [4].

The etiology of ASD is still not fully known [1]. Nevertheless, one of the main factors in the development of ASD are genetics factors [5]. Findings from research indicate that ASD frequently has mitochondrial abnormalities and that autism was associated with several genes [6-7]. Furthermore, it is affirmed that with fragile X syndrome autism is more prevalent [8]. So far researchers did not find any association between neonatal jaundice, and ASD [9].
Nonetheless, other studies claim that genetics factors are the explanation for just 10% of ASD cases, and some copy number variants appear also in the control group but in a reduced occurrence [10].
Environmental and nutritional factors appear to be just as important [1]. Prenatal stress, gestational diabetes, maternal mental illnesses, and prenatal exposure to air pollution, pesticides are among the many factors that increase the likelihood of developing ASD. However, studies suggest that the parents' ages, particularly the father's, are a significant risk factor [5]. Due to Wu S et al research, an increased risk of autism occurs when the parental age is high. Studies claim that the adjusted Odds ratios were 1.41 (95% CI 1.29-1.55) for the mother and 1.55 (95% CI 1.39-1.73) for the father. Moreover, the risk of ASD is increasing even by 18% and 21% when the parental age is increasing by additional 10 years [11].

ASD is considered a chronic condition. It typically first manifests throughout early infancy (3-5 years) [11]. Some of the warning signs are language delay, avoiding eye contact, difficulty expressing emotions, and lack of response to one's name. As a consequence of reaching adulthood, some symptoms, such as abilities in communicating, can become better, but intellectual capacity doesn’t often alter over time [12-13].
There is a triad of features that are linked with ASD. That are irregularity in social development, fixed and strict behavioral patterns, and problems with communication [12]. Some characteristic things about autistic people are that they take words literally, do not understand e.g.idioms, do not like to change their routines, tend to repeat mechanically phrases, and show an intense interest in a narrow field of knowledge [13]. Individuals with ASD exhibit highly varying levels of severity in their symptoms; therefore autism is unique to each person [14].

Pennisi P et al found that in the creative profile of ASD individuals there are some features on a very high level such as detail and originality. Moreover, person with ASD have a higher level of detail than people in control groups. ASD subjects express their originality during linguistic tests as a consequence of the association between creative output and linguistic abilities. However, people with ASD are poor in fluidity and adaptability [15].
Findings from research affirm that autism is a primary contributor to disability in the world. ASD in 100 000 population is responsible for over 58 disability-adjusted life years (DALY) [16]. Moreover, medical comorbidities are frequently present in autistic people [5]. Studies claim that they can more often suffer from neurological issues like epilepsy and cerebral palsy [17-18].

Autism is diagnosed in four years old children on average [5]. That is why an early diagnosis of ASD is crucial for improving their quality of life and lowering lasting costs which are associated with treatments [19]. Notwithstanding, sometimes the diagnosis is inexact due to conventional techniques which include behavioral assessment of autistic people and making conversations with them [20].
Modified Checklist for Autism in Toddlers (M-CHAT) is an example of a screening tool used for assessing the risk of developing ASD in a child. However, some studies imply that present screening techniques can probably not detect every ASD child [21]. That is why other scientists recommend starting screening when children are just 12 months old [22]. Currently, the recommended age range is from 16 to 30 months of age [21]. Recent studies suggest that EEG could be used as an initial biosignature for ASD detection [23]. Besides, Pan PY et al claim that those diagnosed in early infancy with neurological disorders have more risk of following autism [24]. Investigations towards getting to know more about etiology of ASD, are significant for improving treatment and prevention of this disorder [12].

Aim

The aim of this research was to find possible solutions to allieviate behavioral symptoms by targeting exact molecules and states present in ASD people. The focus was to tackle gut microbiota by dietary habits and excercises.

Materials and methods

Research part was done using PubMed database, focusing on the newest articles concerning microbiota, diet, allergy, immunological system and ASD.

Results

The origin of neuroinflammation

Chronic CNS inflammation is a hypothesis gaining popularity in ASD pathology [2, 25-26]. Inflammatory changes correlate with immune dysfunction [2]. Other hypotheses possible in order to distinguish neuroinflammation's origin are: dysregulation of the immune system in the mother during pregnancy, matarnal viral infections during pregnancy, but also overnutrition, maternal stress or psychiatric disorders [2,27]. Another theory concerns the gut-brain axis meaning the central nervous system (CNS) communication with the gastrointestinal tract via the microbiota. This system involves the vagus nerve, the gastrointestinal tract, the immune system, the action of the microbiota and metabolites. Genetic and environmental factors that can alter the composition of the normal gut microbiota predispose to ASD. Confirmation of this theory comes from studies showing that half of ASD patients present

gastrointestinal problems with disrupted gut microbiota. Additionally, gut bacteria modulate, through NLRP3 signaling, inflammatory pathways, which in turn contribute to affecting brain homeostasis. Disruption in the composition of the gut microbiota modulates the immune system and alters blood-brain barrier function [2, 28-29]. Abnormalities in the blood-brain barrier (BBB), including diffusion and cellular transport, may also influence ASD formation [30]. The role of the endocannabinoid system as a major neuromodulatory system involved in regulating emotional responses and cognitive states in ASD pathology is under investigation. Reduced expression of CB1 receptors has been observed in post-mortem studies of individuals with ASD [2].

Structural and functional changes in the brain

Neuroinflammation is a process involving neurons, microglia and macroglia. It is a condition that characterizes many neurodegenerative diseases. Individuals with ASD show signs of altered inflammatory responses, and post mortem studies have documented neuroinflammation in a clique of brain regions - both in the cortex, hippocampus, brainstem and cerebellum. As Li D et al claim that ASD individuals have a greater total volume of white matter and grey matter, but as a consequence of greater volume, their density is decreasing. These differences are most visible in the precentral regions' frontal and temporal lobes. Furthermore, cerebellum and subcortical brain regions like the amygdala or hippocampus also show a volume increase [31]. Neuroinflammation consists of an increase in the reactivity of microglia and astrocyte cells, activation of NO synthase (i-NOS), an increase in the release of cytokines and chemokines [2, 26-27, 32-33]. There are several indicative biomarkers of brain inflammation including: activation of microglia and astrocytes, pro-inflammatory cytokines, activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). The overlapping factors can exacerbate brain inflammation, making it worse [26].

Microglia is a type of glial cell, a macrophage, in addition, it is the primary form of immune defence in the CNS. In the initial phase of activation, it is a pro-inflammatory cell that destroys altered cells or altered proteins, and then changes into an anti-inflammatory cell to repair the resulting damage [26, 34]. In healthy brain tissue, it exists in a resting state, and its shape is described as branched. When it becomes activated it becomes amoeboid due to the processes of phagocytosis of cellular debris and antigens. In patients with ASD, an active form of microglia is observed particularly in the frontal and visual cortex, dorsolateral prefrontal cortex, as well as an increase in the density of microglia cells in the gray matter and an increased volume of microglia soma in the white matter and cerebellum. Activated glial cells secrete pro-inflammatory cytokines such as IL-1β, IL-6 and TNF-α. These cytokines can be toxic to neurons and oligodendrocytes in particular [27, 35]. Excessive activation of glial cells causes inflammation in the brain, which in turn can lead to impaired plasticity of synapses, as well as their degeneration [2, 34-36].

Astrocytes are the main regulators of inflammation in the CNS. In individuals with ASD, they are over-activated, additionally causing increased expression of glial fibrillary acidic protein (GFAP), which is three times higher in children with ASD compared to controls [26].

Immunological system

Pro-inflammatory cytokines (TNF-alpha, such as IL-1β, IL-6, IL-17, IL-12p40 and IL-12p70, granulocyte-macrophage colony-stimulating factor), Th1 cytokine (interferon gamma) and chemokine (Il-8) are elevated in individuals with ASD. Higher levels of IL-12p40 were found

in those with mild disease severity, while elevated TNF- α was found in patients with moderate ASD [2, 26]. Il-6 levels were increased in the frontal cortex and cerebellum of individuals with ASD. Plasma cytokine levels also correlated with ASD symptom severity, meaning that cytokine levels were associated with more impaired communication and aberrant behavior [27].

Nuclear factor Kappa-Light-Chain-Enhancer of activated B cells (NF-κB) is a transcription factor that promotes the expression of inflammatory mediator genes. It mediates the regulation of the cellular immune response by promoting the expression of inflammatory cytokines and chemokines. It also regulates the feedback response that can produce a chronic inflammatory response. Activation of this factor induces production of cytokines, cyclooxygenase-2 (COX-2), inducible nitric oxide synthase (i-NOS) [26].

Markers of inflammation

Changes in lymphocytes subpopulations and accelerated levels of pro-inflammatory cytokines are proofs for immunological dysregulation's presence. C-reactive protein, known as an agent, which level rises in response to inflammation, ameliorates abnormally in people with ASD [37-38]. Spotted changes in lymphocytes subpopulations have been observed within regulatory T cells and Th17 – which levels are accordingly lower and higher in people with ASD in comparison to healthy ones [3]. Insufficient level of Tregs is common in allergy, which occur more often in people with ASD [39-41]. It leads also to lowering TGF-beta 1 level, which shows abnormalities in cytokine's profile. Except for TGF, lower levels of anti-inflammatory cytokines (IL-1Ra, IL-10 and TGF-beta1) [42-43], higher concentrations of pro-inflammatory cytokines (IL-1beta, IL-6, IL-8, MCP-1, IFN-gamma, TNF-alpha) and ameliorated oxidative stress markers are spotted as well [44-45].

Tryptophan and dietary changes

Decreased Tregs' level is caused by indoleamine 2,3- dioxygenase (IDO) – an enzyme, which catalyses tryptophan (Trp) conversion into kynureines. Its altered activity is connected not only with pathologies including neoplasia and autoimmune responses, but also ASD [46-47]. Pro-inflammatory molecules activate IDO-1 enzyme in microglia [48-49]. Kynureine pathway metabolites' levels are dysregulated in ASD: kynurenic acid and Trp levels are lowered, while KYN/KA ratio is higher in comparison to healthy subjects [50-52]. Metabolites of kynureine pathway (KP) due to their neuroactivity are considered as key factors causing neuroinflammation [53].

Trp is known as the one of the most crucial neuromodulators between gut and brain [54]. Findings suggest an impairment in tryptophan metabolism, which consists of two pathways involving strenghtened KP and less active metoxy-indoles pathway – which in normal conditions leads to cerebral's serotonine's and melatonine's production [55]. Serototine is involved in forebrain's development, which structural abnormalities are one of the most consistent anatomical findings reported in ASD [56]. Lowered central serotonin's level associates with increased aggression and excistence of repetitive behaviours [57]. Melatonin prevents iNOS activation and reduces levels of PGE2 [58]. Tryptophan is transported via blood-brain barrier by a competitive transport cannal - common for large neutral amino acids and Trp [59]. Temporary hypoxia and changed blood flow in cerebral's vessels has an impact on tryptophan's uptake rates [51]. Trp level is decreased, as well as their utilization as an energy source in ASD [50, 52, 60-64]. Evidence shows that certain dietary products can rise

Trp's level such as probiotics, magnesium, B vitamins and meditherian diet, which causes improvement in social cognition [63,65-69]. Tryptophan depletion excerbates ASD symptoms – especially worsening of behavioral ones are spotted [70-71].

The role of glutathione in ASD is still being studied. Glutathione is involved in maintaining intracellular redox balance. In ASD, low levels of reduced glutathione and high levels of oxidized glutathione are observed. In addition, abnormalities in the expression of glutathione-related enzymes are noted. Modulation of glutathione is associated with regulation of the redox-sensitive transcription factors nuclear factor kappa B (NF-κB) and activator protein 1 (AP-1), as well as signaling of pro-inflammatory cytokines and inducible enzymes), thus providing an important influence on neuroinflammation [72].

Histaminergic pathway

Altered histaminergic and cholinergic neurotransmission plays a key role in the behavioral phenotype associated with ASD [33].

Histamine acts (HA) by binding to histamine receptors (HR), which are G-protein-coupled receptors known to be H1R-H4R receptors. Activation of the H1R and H2R receptor facilitates the formation of free excitatory postsynaptic potentials. On the other hand, the H3R receptor negatively regulates the synthesis and release of HA - it acts as an auto-receptor controlling the biosynthesis and release of high-affinity histamine or, as a heteroreceptor modulating the release of other brain transmitters including acetylcholine (ACh), dopamine (DA), γ-aminobutyric acid (GABA), glutamate (Glu), serotonin (5-HT) [73-74]. The aforementioned transmitters play a key role in early brain development, but are also likely involved in the onset and progression of ASD [75]. H3R receptor antagonists/inverse agonists improve cognitive skills functioning [73].

The brain histaminergic system (HS) is involved in sleep, wakefulness, cognitive function, sensorimotor function, motor function, and maintenance of homeostasis-both energy and hormonal [76-77].
Histamine is a neurotransmitter, but also an immune modulator. Abnormalities in the histamine pathway result in susceptibility to inflammatory changes due to dysregulation of the neuroimmune response [77].

Reduced histaminergic neurotransmission results in repetitive and tic stereotypy [36]. The most relevant genes for the histamine system are HDC, HNMT (the enzyme responsible for HA metabolism), HRH1, HRH2, HRH3 and HRH4. In a study by Wright C. et al. the expression of HNMT, HRH1, HRH2 and HRH3 genes was significantly altered [36,75].

In patients with ASD, abnormalities are observed in the cholinergic system of the brain, especially in the cholinergic nucleus of the basal forebrain, These changes mainly affected the structure and number of neurons. In addition, a deficiency of choline, which is a precursor molecule for the formation of acetylcholine, and nicotinic cholinergic receptor (nAChR) agonist is observed. Changes in nAChR have also been observed in the thalamus and cerebellum of ASD patients, with the most important change being a decrease in the number of M1 muscarinic receptors [76]. Patients with ASD also show increased quinolinic acid secretion, which increases gluataminergic neurotransmission. This may be due to a 16p11.2 mutation leading to abnormal gluataminergic activity associated with ASD pathogenesis [78].

Physical activity in ASD rehabilitation

An interesting factor regarding ASD is physical activity. Huang J et al claim that physical activity is advantageous for individuals with autism, especially in factors such as motor, and social abilities and it is also helpful in decreasing the severity of autism symptoms in children with ASD. The valuable effect of physical activity is also shown in the advancement of social and communication skills in autistic teenagers [79]. Other studies show that physical activity is beneficial in lowering the count of occurrence of typical conduct in children with autism [80].

Conclusions

ASD is no longer a group of mysterious symptoms – more and more informations about molecular basis in ASD pathogenesis is already known. Presence of immunological dysregulation, changes in the gut microbiota and crucial pathways concerning tryptophan and histaminergic cycles leads us to wider understanding ways, how one can tackle certain molecules in order to allieviate ASD's symptoms. Yet, there is a lot to check to understand ASD's origin and prevent its onset as early as possible. Certain dietary habits and implementing physical excercises into everyday life may allieviate symptoms by lowering immunological inflammation present in ASD.

Bibliography:

[1] Alhowikan, A. M., Al-Ayadhi, L. Y., & Halepoto, D. M. (2019). Impact of environmental pollution, dietary factors and diabetes mellitus on Autism Spectrum Disorder (ASD). *Pakistan journal of medical sciences*, *35*(4), 1179–1184. https://doi.org/10.12669/pjms.35.4.269

[2] Carbone, E., Manduca, A., Cacchione, C., Vicari, S., & Trezza, V. (2021). Healing autism spectrum disorder with cannabinoids: a neuroinflammatory story. *Neuroscience and biobehavioral reviews*, *121*, 128–143. https://doi.org/10.1016/j.neubiorev.2020.12.009

[3] Ellul, P., Rosenzwajg, M., Peyre, H., Fourcade, G., Mariotti-Ferrandiz, E., Trebossen, V., Klatzmann, D., & Delorme, R. (2021). Regulatory T lymphocytes/Th17 lymphocytes imbalance in autism spectrum disorders: evidence from a meta-analysis. *Molecular autism*, *12*(1), 68. https://doi.org/10.1186/s13229-021-00472-4

[4] Loomes, R., Hull, L., & Mandy, W. (2017). What Is the Male-to-Female Ratio in Autism Spectrum Disorder? A Systematic Review and Meta-Analysis. *Journal of the American Academy of Child and Adolescent Psychiatry*, *56*(6), 466–474. https://doi.org/10.1016/j.jaac.2017.03.013

[5] Styles, M., Alsharshani, D., Samara, M., Alsharshani, M., Khattab, A., Qoronfleh, M. W., & Al-Dewik, N. I. (2020). Risk factors, diagnosis, prognosis and treatment of autism. *Frontiers in bioscience (Landmark edition)*, *25*(9), 1682–1717. https://doi.org/10.2741/4873

[6] Varga, N. Á., Pentelényi, K., Balicza, P., Gézsi, A., Reményi, V., Hársfalvi, V., Bencsik, R., Illés, A., Prekop, C., & Molnár, M. J. (2018). Mitochondrial dysfunction and autism: comprehensive genetic analyses of children with autism and mtDNA deletion. *Behavioral and brain functions : BBF*, *14*(1), 4. https://doi.org/10.1186/s12993-018-0135-x

[7] Oztenekecioglu, B., Mavis, M., Osum, M., & Kalkan, R. (2021). Genetic and Epigenetic Alterations in Autism Spectrum Disorder. *Global medical genetics*, *8*(4), 144–148. https://doi.org/10.1055/s-0041-1735540
[8] Marlborough, M., Welham, A., Jones, C., Reckless, S., & Moss, J. (2021). Autism spectrum disorder in females with fragile X syndrome: a systematic review and meta-analysis of prevalence. *Journal of neurodevelopmental disorders*, *13*(1), 28. https://doi.org/10.1186/s11689-021-09362-5
[9] Kujabi, M. L., Petersen, J. P., Pedersen, M. V., Parner, E. T., & Henriksen, T. B. (2021). Neonatal jaundice and autism spectrum disorder: a systematic review and meta-analysis. *Pediatric research*, *90*(5), 934–949. https://doi.org/10.1038/s41390-020-01272-x
[10] Schwartz C. E. (2014). Aberrant tryptophan metabolism: the unifying biochemical basis for autism spectrum disorders?. *Biomarkers in medicine*, *8*(3), 313–315. https://doi.org/10.2217/bmm.14.11
[11] Wu, S., Wu, F., Ding, Y., Hou, J., Bi, J., & Zhang, Z. (2017). Advanced parental age and autism risk in children: a systematic review and meta-analysis. *Acta psychiatrica Scandinavica*, *135*(1), 29–41. https://doi.org/10.1111/acps.12666
[12] Sauer, A. K., Stanton, J. E., Hans, S., & Grabrucker, A. M. (2021). Autism Spectrum Disorders: Etiology and Pathology. In A. M. Grabrucker (Ed.), *Autism Spectrum Disorders*. Exon Publications.
[13] NHS – Signs of autism in children, https://www.nhs.uk/conditions/autism/signs/children/?fbclid=IwAR2oK_1PtgC6OIroEQlDWhZ1f9bdiqftaNqW-WDO_SxbGvAIscGL5KDFZnw access: 11.08.2022
[14] Pendergrass, S., Girirajan, S., & Selleck, S. (2014). Uncovering the etiology of autism spectrum disorders: genomics, bioinformatics, environment, data collection and exploration, and future possibilities. *Pacific Symposium on Biocomputing. Pacific Symposium on Biocomputing*, 422–426.
[15] Pennisi, P., Giallongo, L., Milintenda, G., & Cannarozzo, M. (2021). Autism, autistic traits and creativity: a systematic review and meta-analysis. *Cognitive processing*, *22*(1), 1–36. https://doi.org/10.1007/s10339-020-00992-6
[16] Baxter, A. J., Brugha, T. S., Erskine, H. E., Scheurer, R. W., Vos, T., & Scott, J. G. (2015). The epidemiology and global burden of autism spectrum disorders. *Psychological medicine*, *45*(3), 601–613. https://doi.org/10.1017/S003329171400172X
[17] Davignon, M. N., Qian, Y., Massolo, M., & Croen, L. A. (2018). Psychiatric and Medical Conditions in Transition-Aged Individuals With ASD. *Pediatrics*, *141*(Suppl 4), S335–S345. https://doi.org/10.1542/peds.2016-4300K
[18] Schendel, D. E., Overgaard, M., Christensen, J., Hjort, L., Jørgensen, M., Vestergaard, M., & Parner, E. T. (2016). Association of Psychiatric and Neurologic Comorbidity With Mortality Among Persons With Autism Spectrum Disorder in a Danish Population. *JAMA pediatrics*, *170*(3), 243–250. https://doi.org/10.1001/jamapediatrics.2015.3935
[19] Hossain, M. D., Kabir, M. A., Anwar, A., & Islam, M. Z. (2021). Detecting autism spectrum disorder using machine learning techniques: An experimental analysis on toddler, child, adolescent and adult datasets. *Health information science and systems*, *9*(1), 17. https://doi.org/10.1007/s13755-021-00145-9
[20] Bi, X. A., Liu, Y., Jiang, Q., Shu, Q., Sun, Q., & Dai, J. (2018). The Diagnosis of Autism Spectrum Disorder Based on the Random Neural Network Cluster. *Frontiers in human neuroscience*, *12*, 257. https://doi.org/10.3389/fnhum.2018.00257

[21] Wallis, K. E., & Guthrie, W. (2020). Identifying Autism Spectrum Disorder in Real-World Health Care Settings. *Pediatrics*, *146*(2), e20201467. https://doi.org/10.1542/peds.2020-1467
[22] Wieckowski, A. T., Hamner, T., Nanovic, S., Porto, K. S., Coulter, K. L., Eldeeb, S. Y., Chen, C. A., Fein, D. A., Barton, M. L., Adamson, L. B., & Robins, D. L. (2021). Early and Repeated Screening Detects Autism Spectrum Disorder. *The Journal of pediatrics*, *234*, 227–235. https://doi.org/10.1016/j.jpeds.2021.03.009
[23] O'Neill, M., & Shear, T. (2018). EEG for Diagnosis of Autism Spectrum Disorder. *Pediatric neurology briefs*, *32*, 13. https://doi.org/10.15844/pedneurbriefs-32-13
[24] Pan, P. Y., Bölte, S., Kaur, P., Jamil, S., & Jonsson, U. (2021). Neurological disorders in autism: A systematic review and meta-analysis. *Autism : the international journal of research and practice*, *25*(3), 812–830. https://doi.org/10.1177/1362361320951370
[25] Matta, S. M., Hill-Yardin, E. L., & Crack, P. J. (2019). The influence of neuroinflammation in Autism Spectrum Disorder. *Brain, behavior, and immunity*, *79*, 75–90. https://doi.org/10.1016/j.bbi.2019.04.037
[26] Kern, J. K., Geier, D. A., Sykes, L. K., & Geier, M. R. (2016). Relevance of Neuroinflammation and Encephalitis in Autism. *Frontiers in cellular neuroscience*, *9*, 519. https://doi.org/10.3389/fncel.2015.00519
[27] Toscano, C., Barros, L., Lima, A. B., Nunes, T., Carvalho, H. M., & Gaspar, J. M. (2021). Neuroinflammation in autism spectrum disorders: Exercise as a "pharmacological" tool. *Neuroscience and biobehavioral reviews*, *129*, 63–74. https://doi.org/10.1016/j.neubiorev.2021.07.023
[28] Pellegrini, C., Antonioli, L., Calderone, V., Colucci, R., Fornai, M., & Blandizzi, C. (2020). Microbiota-gut-brain axis in health and disease: Is NLRP3 inflammasome at the crossroads of microbiota-gut-brain communications?. *Progress in neurobiology*, *191*, 101806. https://doi.org/10.1016/j.pneurobio.2020.101806
[29] Doroszkiewicz, J., Groblewska, M., & Mroczko, B. (2021). The Role of Gut Microbiota and Gut-Brain Interplay in Selected Diseases of the Central Nervous System. *International journal of molecular sciences*, *22*(18), 10028. https://doi.org/10.3390/ijms221810028
[30] Kealy, J., Greene, C., & Campbell, M. (2020). Blood-brain barrier regulation in psychiatric disorders. *Neuroscience letters*, *726*, 133664. https://doi.org/10.1016/j.neulet.2018.06.033
[31] Li, D., Karnath, H. O., & Xu, X. (2017). Candidate Biomarkers in Children with Autism Spectrum Disorder: A Review of MRI Studies. *Neuroscience bulletin*, *33*(2), 219–237. https://doi.org/10.1007/s12264-017-0118-1
[32] Bauman, M. L., & Kemper, T. L. (2005). Neuroanatomic observations of the brain in autism: a review and future directions. *International journal of developmental neuroscience : the official journal of the International Society for Developmental Neuroscience*, *23*(2-3), 183–187. https://doi.org/10.1016/j.ijdevneu.2004.09.006
[33] Eissa, N., Sadeq, A., Sasse, A., & Sadek, B. (2020). Role of Neuroinflammation in Autism Spectrum Disorder and the Emergence of Brain Histaminergic System. Lessons Also for BPSD?. *Frontiers in pharmacology*, *11*, 886. https://doi.org/10.3389/fphar.2020.00886
[34] Liao, X., Yang, J., Wang, H., & Li, Y. (2020). Microglia mediated neuroinflammation in autism spectrum disorder. *Journal of psychiatric research*, *130*, 167–176. https://doi.org/10.1016/j.jpsychires.2020.07.013
[35] Kim, Y. S., Choi, J., & Yoon, B. E. (2020). Neuron-Glia Interactions in Neurodevelopmental Disorders. *Cells*, *9*(10), 2176. https://doi.org/10.3390/cells9102176

[36] Wright, C., Shin, J. H., Rajpurohit, A., Deep-Soboslay, A., Collado-Torres, L., Brandon, N. J., Hyde, T. M., Kleinman, J. E., Jaffe, A. E., Cross, A. J., & Weinberger, D. R. (2017). Altered expression of histamine signaling genes in autism spectrum disorder. *Translational psychiatry*, *7*(5), e1126. https://doi.org/10.1038/tp.2017.87
[37] Yin, F., Wang, H., Liu, Z., & Gao, J. (2020). Association between peripheral blood levels of C-reactive protein and Autism Spectrum Disorder in children: A systematic review and meta-analysis. *Brain, behavior, and immunity*, *88*, 432–441. https://doi.org/10.1016/j.bbi.2020.04.008
[38] Nadeem, R., Hussain, T., & Sajid, H. (2020). C reactive protein elevation among children or among mothers' of children with autism during pregnancy, a review and meta-analysis. *BMC psychiatry*, *20*(1), 251. https://doi.org/10.1186/s12888-020-02619-8
[39] Turner, J. A., Stephen-Victor, E., Wang, S., Rivas, M. N., Abdel-Gadir, A., Harb, H., Cui, Y., Fanny, M., Charbonnier, L. M., Fong, J., Benamar, M., Wang, L., Burton, O. T., Bansal, K., Bry, L., Zhu, C., Li, Q. Z., Clement, R. L., Oettgen, H. C., Crestani, E., … Chatila, T. A. (2020). Regulatory T Cell-Derived TGF-β1 Controls Multiple Checkpoints Governing Allergy and Autoimmunity. *Immunity*, *53*(6), 1202–1214.e6. https://doi.org/10.1016/j.immuni.2020.10.002
[40] Braga, M., Quecchia, C., Cavallucci, E., Di Giampaolo, L., Schiavone, C., Petrarca, C., & Di Gioacchino, M. (2011). T regulatory cells in allergy. *International journal of immunopathology and pharmacology*, *24*(1 Suppl), 55S–64S.
[41] Li, H., Liu, H., Chen, X., Zhang, J., Tong, G., & Sun, Y. (2021). Association of food hypersensitivity in children with the risk of autism spectrum disorder: a meta-analysis. *European journal of pediatrics*, *180*(4), 999–1008. https://doi.org/10.1007/s00431-020-03826-x
[42] Masi, A., Quintana, D. S., Glozier, N., Lloyd, A. R., Hickie, I. B., & Guastella, A. J. (2015). Cytokine aberrations in autism spectrum disorder: a systematic review and meta-analysis. *Molecular psychiatry*, *20*(4), 440–446. https://doi.org/10.1038/mp.2014.59
[43] Saghazadeh, A., Ataeinia, B., Keynejad, K., Abdolalizadeh, A., Hirbod-Mobarakeh, A., & Rezaei, N. (2019). Anti-inflammatory cytokines in autism spectrum disorders: A systematic review and meta-analysis. *Cytokine*, *123*, 154740. https://doi.org/10.1016/j.cyto.2019.154740
[44] Saghazadeh, A., Ataeinia, B., Keynejad, K., Abdolalizadeh, A., Hirbod-Mobarakeh, A., & Rezaei, N. (2019). A meta-analysis of pro-inflammatory cytokines in autism spectrum disorders: Effects of age, gender, and latitude. *Journal of psychiatric research*, *115*, 90–102. https://doi.org/10.1016/j.jpsychires.2019.05.019
[45] Chen, L., Shi, X. J., Liu, H., Mao, X., Gui, L. N., Wang, H., & Cheng, Y. (2021). Oxidative stress marker aberrations in children with autism spectrum disorder: a systematic review and meta-analysis of 87 studies (N = 9109). *Translational psychiatry*, *11*(1), 15. https://doi.org/10.1038/s41398-020-01135-3
[46] Platten, M., Ho, P. P., Youssef, S., Fontoura, P., Garren, H., Hur, E. M., Gupta, R., Lee, L. Y., Kidd, B. A., Robinson, W. H., Sobel, R. A., Selley, M. L., & Steinman, L. (2005). Treatment of autoimmune neuroinflammation with a synthetic tryptophan metabolite. *Science (New York, N.Y.)*, *310*(5749), 850–855. https://doi.org/10.1126/science.1117634
[47] Katz, J. B., Muller, A. J., & Prendergast, G. C. (2008). Indoleamine 2,3-dioxygenase in T-cell tolerance and tumoral immune escape. *Immunological reviews*, *222*, 206–221. https://doi.org/10.1111/j.1600-065X.2008.00610.x
[48] Pallotta, M. T., Orabona, C., Volpi, C., Grohmann, U., Puccetti, P., & Fallarino, F. (2010). Proteasomal Degradation of Indoleamine 2,3-Dioxygenase in CD8 Dendritic Cells is

Mediated by Suppressor of Cytokine Signaling 3 (SOCS3). *International journal of tryptophan research : IJTR*, *3*, 91–97. https://doi.org/10.4137/ijtr.s3971
[49] Anderson, G., & Maes, M. (2014). Redox Regulation and the Autistic Spectrum: Role of Tryptophan Catabolites, Immuno-inflammation, Autoimmunity and the Amygdala. *Current neuropharmacology*, *12*(2), 148–167. https://doi.org/10.2174/1570159X11666131120223757
[50] Bryn, V., Verkerk, R., Skjeldal, O. H., Saugstad, O. D., & Ormstad, H. (2017). Kynurenine Pathway in Autism Spectrum Disorders in Children. *Neuropsychobiology*, *76*(2), 82–88. https://doi.org/10.1159/000488157
[51] Bilgiç, A., Abuşoğlu, S., Sadıç Çelikkol, Ç., Oflaz, M. B., Akça, Ö. F., Sivrikaya, A., Baysal, T., & Ünlü, A. (2022). Altered kynurenine pathway metabolite levels in toddlers and preschool children with autism spectrum disorder. *The International journal of neuroscience*, *132*(8), 826–834. https://doi.org/10.1080/00207454.2020.1841187
[52] Carpita, B., Nardi, B., Palego, L., Cremone, I. M., Massimetti, G., Carmassi, C., Betti, L., Giannaccini, G., & Dell'Osso, L. (2022). Kynurenine pathway and autism spectrum phenotypes: an investigation among adults with autism spectrum disorder and their first-degree relatives. *CNS spectrums*, 1–12. Advance online publication. https://doi.org/10.1017/S1092852922000840
[53] Hilmas, C., Pereira, E. F., Alkondon, M., Rassoulpour, A., Schwarcz, R., & Albuquerque, E. X. (2001). The brain metabolite kynurenic acid inhibits alpha7 nicotinic receptor activity and increases non-alpha7 nicotinic receptor expression: physiopathological implications. *The Journal of neuroscience : the official journal of the Society for Neuroscience*, *21*(19), 7463–7473. https://doi.org/10.1523/JNEUROSCI.21-19-07463.2001
[54] Cryan, J. F., O'Riordan, K. J., Cowan, C., Sandhu, K. V., Bastiaanssen, T., Boehme, M., Codagnone, M. G., Cussotto, S., Fulling, C., Golubeva, A. V., Guzzetta, K. E., Jaggar, M., Long-Smith, C. M., Lyte, J. M., Martin, J. A., Molinero-Perez, A., Moloney, G., Morelli, E., Morillas, E., O'Connor, R., … Dinan, T. G. (2019). The Microbiota-Gut-Brain Axis. *Physiological reviews*, *99*(4), 1877–2013. https://doi.org/10.1152/physrev.00018.2018
[55] Savino, R., Carotenuto, M., Polito, A. N., Di Noia, S., Albenzio, M., Scarinci, A., Ambrosi, A., Sessa, F., Tartaglia, N., & Messina, G. (2020). Analyzing the Potential Biological Determinants of Autism Spectrum Disorder: From Neuroinflammation to the Kynurenine Pathway. *Brain sciences*, *10*(9), 631. https://doi.org/10.3390/brainsci10090631
[56] Casanova M. F. (2007). The neuropathology of autism. *Brain pathology (Zurich, Switzerland)*, *17*(4), 422–433. https://doi.org/10.1111/j.1750-3639.2007.00100.x
[57] Mosienko, V., Bert, B., Beis, D., Matthes, S., Fink, H., Bader, M., & Alenina, N. (2012). Exaggerated aggression and decreased anxiety in mice deficient in brain serotonin. *Translational psychiatry*, *2*(5), e122. https://doi.org/10.1038/tp.2012.44
[58] Mayo, J. C., Sainz, R. M., Tan, D. X., Hardeland, R., Leon, J., Rodriguez, C., & Reiter, R. J. (2005). Anti-inflammatory actions of melatonin and its metabolites, N1-acetyl-N2-formyl-5-methoxykynuramine (AFMK) and N1-acetyl-5-methoxykynuramine (AMK), in macrophages. *Journal of neuroimmunology*, *165*(1-2), 139–149. https://doi.org/10.1016/j.jneuroim.2005.05.002
[59] Kennett, G. A., Curzon, G., Hunt, A., & Patel, A. J. (1986). Immobilization decreases amino acid concentrations in plasma but maintains or increases them in brain. *Journal of neurochemistry*, *46*(1), 208–212. https://doi.org/10.1111/j.1471-4159.1986.tb12947.x
[60] Anderson G. M. (2002). Genetics of childhood disorders: XLV. Autism, part 4: serotonin in autism. *Journal of the American Academy of Child and Adolescent Psychiatry*, *41*(12), 1513–1516. https://doi.org/10.1097/00004583-200212000-00025

[61] Rossignol, D. A., & Frye, R. E. (2011). Melatonin in autism spectrum disorders: a systematic review and meta-analysis. *Developmental medicine and child neurology*, *53*(9), 783–792. https://doi.org/10.1111/j.1469-8749.2011.03980.x
[62] D'Eufemia, P., Finocchiaro, R., Celli, M., Viozzi, L., Monteleone, D., & Giardini, O. (1995). Low serum tryptophan to large neutral amino acids ratio in idiopathic infantile autism. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *49*(6), 288–292. https://doi.org/10.1016/0753-3322(96)82645-X
[63] Kałużna-Czaplińska, J., Jóźwik-Pruska, J., Chirumbolo, S., & Bjørklund, G. (2017). Tryptophan status in autism spectrum disorder and the influence of supplementation on its level. *Metabolic brain disease*, *32*(5), 1585–1593. https://doi.org/10.1007/s11011-017-0045-x
[64] Boccuto, L., Chen, C. F., Pittman, A. R., Skinner, C. D., McCartney, H. J., Jones, K., Bochner, B. R., Stevenson, R. E., & Schwartz, C. E. (2013). Decreased tryptophan metabolism in patients with autism spectrum disorders. *Molecular autism*, *4*(1), 16. https://doi.org/10.1186/2040-2392-4-16
[65] Zhu, C., Sawrey-Kubicek, L., Beals, E., Rhodes, C. H., Houts, H. E., Sacchi, R., & Zivkovic, A. M. (2020). Human gut microbiome composition and tryptophan metabolites were changed differently by fast food and Mediterranean diet in 4 days: a pilot study. *Nutrition research (New York, N.Y.)*, *77*, 62–72. https://doi.org/10.1016/j.nutres.2020.03.005
[66] Ugartemendia, L., Bravo, R., Reuter, M., Castaño, M. Y., Plieger, T., Zamoscik, V., Kirsch, P., & Rodríguez, A. B. (2021). SLC6A4 polymorphisms modulate the efficacy of a tryptophan-enriched diet on age-related depression and social cognition. *Clinical nutrition (Edinburgh, Scotland)*, *40*(4), 1487–1494. https://doi.org/10.1016/j.clnu.2021.02.023
[67] Kikuchi, A. M., Tanabe, A., & Iwahori, Y. (2021). A systematic review of the effect of L-tryptophan supplementation on mood and emotional functioning. *Journal of dietary supplements*, *18*(3), 316–333. https://doi.org/10.1080/19390211.2020.1746725
[68] Purton, T., Staskova, L., Lane, M. M., Dawson, S. L., West, M., Firth, J., Clarke, G., Cryan, J. F., Berk, M., O'Neil, A., Dean, O., Hadi, A., Honan, C., & Marx, W. (2021). Prebiotic and probiotic supplementation and the tryptophan-kynurenine pathway: A systematic review and meta analysis. *Neuroscience and biobehavioral reviews*, *123*, 1–13. https://doi.org/10.1016/j.neubiorev.2020.12.026
[69] Zamoscik, V., Schmidt, S., Bravo, R., Ugartemendia, L., Plieger, T., Rodríguez, A. B., Reuter, M., & Kirsch, P. (2021). Tryptophan-enriched diet or 5-hydroxytryptophan supplementation given in a randomized controlled trial impacts social cognition on a neural and behavioral level. *Scientific reports*, *11*(1), 21637. https://doi.org/10.1038/s41598-021-01164-y
[70] McDougle, C. J., Naylor, S. T., Cohen, D. J., Aghajanian, G. K., Heninger, G. R., & Price, L. H. (1996). Effects of tryptophan depletion in drug-free adults with autistic disorder. *Archives of general psychiatry*, *53*(11), 993–1000. https://doi.org/10.1001/archpsyc.1996.01830110029004
[71] Monda, V., Salerno, M., Sessa, F., Bernardini, R., Valenzano, A., Marsala, G., Zammit, C., Avola, R., Carotenuto, M., Messina, G., & Messina, A. (2018). Functional Changes of Orexinergic Reaction to Psychoactive Substances. *Molecular neurobiology*, *55*(8), 6362–6368. https://doi.org/10.1007/s12035-017-0865-z
[72] Bjørklund, G., Tinkov, A. A., Hosnedlová, B., Kizek, R., Ajsuvakova, O. P., Chirumbolo, S., Skalnaya, M. G., Peana, M., Dadar, M., El-Ansary, A., Qasem, H., Adams, J. B., Aaseth, J., & Skalny, A. V. (2020). The role of glutathione redox imbalance in autism spectrum

disorder: A review. *Free radical biology & medicine*, *160*, 149–162. https://doi.org/10.1016/j.freeradbiomed.2020.07.017
[73] Eissa, N., Azimullah, S., Jayaprakash, P., Jayaraj, R. L., Reiner, D., Ojha, S. K., Beiram, R., Stark, H., Łażewska, D., Kieć-Kononowicz, K., & Sadek, B. (2019). The dual-active histamine H3 receptor antagonist and acetylcholine esterase inhibitor E100 ameliorates stereotyped repetitive behavior and neuroinflammmation in sodium valproate induced autism in mice. *Chemico-biological interactions*, *312*, 108775. https://doi.org/10.1016/j.cbi.2019.108775
[74] Venkatachalam, K., Eissa, N., Awad, M. A., Jayaprakash, P., Zhong, S., Stölting, F., Stark, H., & Sadek, B. (2021). The histamine H3R and dopamine D2R/D3R antagonist ST-713 ameliorates autism-like behavioral features in BTBR T+tf/J mice by multiple actions. *Biomedicine & pharmacotherapy = Biomedecine & pharmacotherapie*, *138*, 111517. https://doi.org/10.1016/j.biopha.2021.111517
[75] Eissa, N., Venkatachalam, K., Jayaprakash, P., Falkenstein, M., Dubiel, M., Frank, A., Reiner-Link, D., Stark, H., & Sadek, B. (2021). The Multi-Targeting Ligand ST-2223 with Histamine H3 Receptor and Dopamine D2/D3 Receptor Antagonist Properties Mitigates Autism-Like Repetitive Behaviors and Brain Oxidative Stress in Mice. *International journal of molecular sciences*, *22*(4), 1947. https://doi.org/10.3390/ijms22041947
[76] Eissa, N., Jayaprakash, P., Stark, H., Łażewska, D., Kieć-Kononowicz, K., & Sadek, B. (2020). Simultaneous Blockade of Histamine H3 Receptors and Inhibition of Acetylcholine Esterase Alleviate Autistic-Like Behaviors in BTBR T+ tf/J Mouse Model of Autism. *Biomolecules*, *10*(9), 1251. https://doi.org/10.3390/biom10091251
[77] Frick, L., Rapanelli, M., Abbasi, E., Ohtsu, H., & Pittenger, C. (2016). Histamine regulation of microglia: Gene-environment interaction in the regulation of central nervous system inflammation. *Brain, behavior, and immunity*, *57*, 326–337. https://doi.org/10.1016/j.bbi.2016.07.002
[78] Lim, C. K., Essa, M. M., de Paula Martins, R., Lovejoy, D. B., Bilgin, A. A., Waly, M. I., Al-Farsi, Y. M., Al-Sharbati, M., Al-Shaffae, M. A., & Guillemin, G. J. (2016). Altered kynurenine pathway metabolism in autism: Implication for immune-induced glutamatergic activity. *Autism research : official journal of the International Society for Autism Research*, *9*(6), 621–631. https://doi.org/10.1002/aur.1565
[79] Huang, J., Du, C., Liu, J., & Tan, G. (2020). Meta-Analysis on Intervention Effects of Physical Activities on Children and Adolescents with Autism. *International journal of environmental research and public health*, *17*(6), 1950. https://doi.org/10.3390/ijerph17061950
[80] Ferreira, J. P., Ghiarone, T., Júnior, C., Furtado, G. E., Carvalho, H. M., Rodrigues, A. M., & Toscano, C. (2019). Effects of Physical Exercise on the Stereotyped Behavior of Children with Autism Spectrum Disorders. *Medicina (Kaunas, Lithuania)*, *55*(10), 685. https://doi.org/10.3390/medicina55100685