neuroglia

MDPI

Hypothesis

On the Potential Therapeutic Roles of Taurine in Autism Spectrum Disorder

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Abstract: Contemporary research has found that people with autism spectrum disorder (ASD) exhibit aberrant immunological function, with a shift toward increased cytokine production and unusual cell function. Microglia and astroglia were found to be significantly activated in immuno-cytochemical studies, and cytokine analysis revealed that the macrophage chemoattractant protein-1 (MCP-1), interleukin 6 (IL-6), tumor necrosis factor α (TNF-α), and transforming growth factor β-1 (TGFB-1), all generated in the neuroglia, constituted the most predominant cytokines in the brain. Taurine (2-aminoethanesulfonic acid) is a promising therapeutic molecule able to increase the activity of antioxidant enzymes and ATPase, which may be protective against aluminum-induced neurotoxicity. It can also stimulate neurogenesis, synaptogenesis, and reprogramming of proinflammatory M1 macrophage polarization by decreasing mitophagy (mitochondrial autophagy) and raising the expression of the markers of the anti-inflammatory and pro-healing M2 macrophages, such as macrophage mannose receptor (MMR, CD206) and interleukin 10 (IL-10), while lowering the expression of the M1 inflammatory factor genes. Taurine also induces autophagy, which is a mechanism that is impaired in microglia cells and is critically associated with the pathophysiology of ASD. We hypothesize here that taurine could reprogram the metabolism of M1 macrophages that are overstimulated in the nervous system of people suffering from ASD, thereby decreasing the neuroinflammatory process characterized by autophagy impairment (due to excessive microglia activation), neuronal death, and improving cognitive functions. Therefore, we suggest that taurine can serve as an important lead for the development of novel drugs for ASD treatment.

Keywords: autism; autism spectrum disorder; autophagy; macrophage polarization; neurogenesis; taurine

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1. Introduction

The term autism was created in 1911 by the psychiatrist Paul Eugen Bleuler (1857–1939), who employed the Greek word "self" to reflect one's desire to retire into one's thoughts [1]. Social difficulties, communication problems, an absence of social bonding behaviors, and the prevalence of repetitive behaviors are all symptoms of this disease [2]. Although several studies [3–5] have been dedicated to finding the genetic mechanisms of ASD, the majority of diagnosed cases are still unexplained [6]. It has been claimed that a range of gene–environment interactions, epigenetic changes, and environmental variables all have important and distinct roles in the genesis of ASD [7]. For example, prenatal, perinatal, and postnatal environment influences are considered to be responsible for 60% of the risk of ASD, whereas genetic features account for the remaining 35–40% [8]. A tendency

toward increased cytokine release and unusual immune cell functions have been demonstrated in people with ASD in several investigations [9–14]. There is also proof that most of these abnormal immunological patterns are linked to the worsening of autistic behavior [14]. Even when the neurobiological origin of ASD is multifactorial, neuroinflammatory processes are thought to contribute to the formation of autistic behavioral alterations [15,16], and convincing research evidence indicates that microglial stimulation or disturbance can have a significant impact on neural development, leading to disorders in neuronal growth, such as ASD [17]. Basic research continues to be undertaken to identify the causes that promote the development of ASD. However, most of this research is oriented more toward the search for the causes of the disease than toward the development of effective medicines. As a result, children with ASD still do not have specific treatments capable of stopping the progressive neurodegeneration that some are affected by. This work provides the scientific rationale for the potential therapeutic utilization of taurine for patients with ASD.

2. Microglial Activation in ASD

The central nervous system (CNS) contains a specialized population of macrophage-like cells known as microglia. Considered to be immune sentinels that are capable of orchestrating a potent inflammatory response, microglia can perform a variety of functions in various periods of life, both in normal and pathological conditions [18]. Microglia have a multitude of roles [19] throughout CNS maturation, such as phagocytic action during neuronal/synaptic development (most likely reflected in the elimination of repetitive neurons and synapses); this process is also known as "synaptic pruning" [17]. Appealing scientific proof implies that microglial activation or malfunction can have a significant impact on neuron maturation by reducing synaptic pruning, eventually leading to neurodevelopmental dysfunction, such as ASD [17].

Microglia, like macrophages, respond to CNS injuries by adopting distinct activated profiles [20]. When microglial cells are activated, they undergo phenotypical changes, migrate to the injured area, and proliferate (i.e., undergo microgliosis), as well as enhancing the synthesis of many proteins, including immunological intermediaries [17]. The standard, classically activated inflammatory and neurotoxic M1 macrophages, as well as the alternatively activated anti-inflammatory M2 macrophages, were described in [20–22].

3. M1 Polarization in ASD

Classically activated M1 macrophages are known to mediate excessive inflammatory responses, cytotoxicity, and tissue damage. They mediate the host's defense against several bacterial, viral, and protozoal pathogens. Furthermore, aluminum from vaccines [23], bacterial lipopolysaccharide (LPS) [24,25], TNF-α [26], interferon γ (IFN-γ) [27], Aβ oligomers [27,28], and α-synuclein [29,30] are able to promote the M1 phenotype. "The induction of mitogen-activated protein kinase (ERK1/2 and p38), synthesis of MHC-II (major histocompatibility complex type II) cell membrane glycoprotein, the release of inflammatory cytokines (TNF-α, Interleukin-1 (IL-1), IL-6, and IL-12), and production of reactive oxygen species are all hallmarks of the classic M1 phenotype" [25].

Increased glutaminase, inducible nitric oxide (NO) synthase, (iNOS or NOS2), and inducible COX-2 (cyclooxygenase 2) synthesis leads to increased NO, glutamate, and prostaglandins release, respectively. Most of the factors released by microglia are neurotoxic for neuronal cell cultures [31]. The cytokines Interleukin 4 (IL-4) and IL-13, which are released from Th2 lymphocytes, can generate the alternative M2 profile in embryonic microglial cells [32]. In vitro, IL-4 reduces iNOS activity, TNF-α, and superoxide release in LPS and TNF-α-stimulated microglial cells, as well as protecting neurons against neuronal toxicity [33]. Microglial activation in human autistic brains was documented in several studies (for review see [17]). Active inflammatory mechanisms were detected within the brain cortex, white matter, and significantly in the cerebellum, according to neuropathological investigations of autistic brains [34].

Microglial and astroglial cells were significantly stimulated in immunological and cytochemical experiments, and cytokine profiles revealed both monocyte chemoattractant protein 1 (MCP-1, also known as C-C motif ligand 2, CCL2) and transforming growth factor β-1 (TGFB-1), which are produced by neuroglia cells, are abundant cytokines in the brain [34]. Furthermore, IL-6 was found to be very much elevated in the anterior cingulated cortex, and in the spinal fluid of individuals with ASD in recent studies [34,35]. It was claimed that increased IL-6 levels in the autistic brain induce instability of neuronal networks by affecting neural cell bonding and synapse establishment, and so contribute to ASD development [35]. Myeloid cells (which are a subgroup of leukocytes that includes dendritic cells (DCs), granulocytes, macrophages, and monocytes [36]) seem to make an important contribution to the pathophysiology of ASD in children, according to the research [37]. In the brains of children with ASD, immunohistochemistry indicated higher amounts of microglial cells in the parenchyma, an increased number of macrophages surrounding the vascular space, and heightened microglial and perivascular macrophage activation, as well as increased amounts of MCP-1 [34,38].

Growing amounts of monocytic leucocytes in the plasma and elevated cytokines released after toll-like receptor 4 (TLR4) stimulation in monocytes of individuals with ASD, together with the elevated concentrations of IL-1, IL-6, and IL-23, and correlations with behavioral evaluations have been found in studies examining peripheral myeloid activity, which are compatible with the study results in the brain [10,39,40]. Evidence has been provided of aberrant dispersion of dendritic cell density in children with ASD, similar to results in microglial cells and monocytes, thus implying that multiple lineages of the myeloid tissue are damaged in the disease [37].

A comprehensive investigation was conducted to find inflammatory signs that could be used for ASD diagnostics. In cultivated M1 and M2 macrophages obtained from individuals with ASD (n = 29) and normally developing persons (n = 30), the messenger RNA production of cytokines that involved TNF-α was assessed. TNF-α production in the M1 subtype was much greater in ASD individuals than in normal people, but this elevation was not detected in M2 macrophages [41].

4. Taurine Reprograms Macrophage M1 Polarization to the M2 Phenotype

Macrophage metabolism has historically been recognized to be highly malleable, reflecting pathologies related to distinct disease states [42–44]. In relatively recent times, ambient signals and the surrounding cytokine microenvironment were assumed to be in control of macrophage metabolic reactions, partially due to an old idea that all macrophages originated in the blood [45,46]. The M1 and M2 macrophages paradigm hypothesized that these cells in a resting phase of M0 may be transformed to M1 or M2 modes by exposing them to some specific cytokines [47]. However, a recent report outlined the fundamental metabolic and physiological distinctions between M1 and M2 macrophage polarization modes in laboratory settings [21].

M1 macrophages, which are stimulated by TNF-α or IFN-γ, exhibit a significant increase in the glycolytic metabolism to generate adenosine triphosphate (ATP) for phagocytic and microbicidal activities, while the mitochondrial tricarboxylic acid cycle (TCA cycle) is blocked. M2 macrophages, on the other hand, which are stimulated by IL-4 and IL-13, possess a working TCA circuit and increased mitochondrial oxidative phosphorylation (OXPHOS) capacity. Chemicals that reduce inflammation, such as steroids, IL-10, IL-13, and colony-stimulating factor 1 (CSF-1) are usually related to the M2 macrophage phenotype [21].

The reconfiguration of a macrophage from the M1 to M2 phenotype could be performed by focusing on their metabolism: according to the experimental evidence, reconnecting the metabolism to mitochondrial oxidative phosphorylation prevents the inflammation process (M1 state). As a result, modulation of the energy metabolism represents a promising option for the therapy of inflammatory disorders [48]. Taurine (an amino sulfonic acid, which is widely distributed in animal tissues, accounting for up to 0.1% of total

human body weight) inhibits macrophage M1 polarization by suppressing mitophagy (mitochondrial autophagy), which reduces the expression of the M1 inflammatory genes, while raising the synthesis of the M2 markers (CD206 and IL-10), according to a recent study. Taurine also reconfigures the M1 macrophage power metabolism by preserving an elevated number of mitochondria that prevent the switch to glycolysis, which is essential for the M1 macrophages [48].

In this respect, taurine-chloramine inhibits macrophage release of inflammation promoters, such as macrophage inflammatory protein 2 (MIP-2, also known as chemokine CXC ligand 2, CXCL-2), MCP-1, MCP-2, TNF-α, IL-6, nitric oxide, nitrites, and prostaglandin E2 (PGE2) [49–54]. Taurine-chloramine also stimulates the synthesis of the nuclear factor erythroid 2-related factor 2 (NRF-2), which is a transcription factor that controls the production of important detoxification and antioxidant enzymes [55]. Importantly, these inflammation-promoting cytokines were shown to be significantly elevated in the brains of children with ASD. Since taurine administration was shown to inhibit the release of these cytokines, one can infer that taurine may have an important therapeutic action.

5. Taurine Decreases the Activation State of Microglia

Taurine (or 2-aminoethanesulfonic acid) is an amino acid, which is naturally derived from sulfur amino acids, such as methionine and cysteine, and which is not employed in protein biosynthesis. The enzyme cysteine sulfinic acid decarboxylase (CSD) synthesizes it from cysteine and methionine in the kidney, liver, and nerve cells, specifically in glial cells [56]. Taurine is three to four times more abundant in the growing brain compared with the adult brain [57], and its amount diminishes with age, implying that taurine exerts an essential function during neuronal maturation [58].

Anti-inflammatory effects are also known to be exerted by taurine [50,51,59–61]. In this regard, taurine was shown to decrease the amount of microglia-stimulated cells in elderly mice (Figure 1) [62]. In taurine-treated animals, stimulated microglia cells constituted 8.2% of the whole microglia, while in sodium chloride (NaCl)-treated animals, they constituted 37.8% [62].

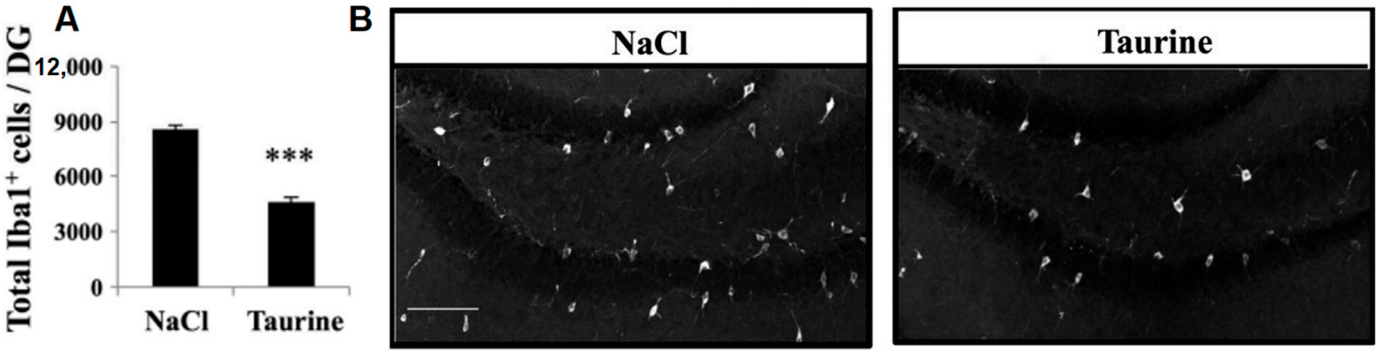

Figure 1. Taurine reduced the number of microglia and indicators of microglia activation. (**A**) Histogram displaying the total number of cells in the dentate gyrus of the hippocampus. *** Bilateral Student's *t*-test $p < 0.001$. Each value represents the mean ± SEM (standard error of the mean). (**B**) Confocal micrographs of the hippocampal sections immunostained for MHC-II (major histocompatibility complex II molecules). Reproduced from Gebara E, Udry F, Sultan S, & Toni N. Taurine increases hippocampal neurogenesis in aging mice. Stem cell research. 2015; 14 (3), 369–379 (Ref. [62]). This figure is reproduced from an open access article distributed under the terms of the Creative Commons CC-BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Microglia undergo structural alterations as a consequence of brain inflammation. Here, resting microglia (phase I) have stick-formed cellular soma with tiny, bifurcated dendrites, while activated microglia (phase II) have enlarged cellular soma with extended and dumpy dendrites (Figure 2). The structure of microglial cells in taurine-treated and reference

rats was also studied by Gebara and colleagues. Taurine therapy reduced the soma size, expanded the territorial projection area, and increased the number of microglia dendrites; these structural variations are associated with a lowered stimulated state of microglia [62].

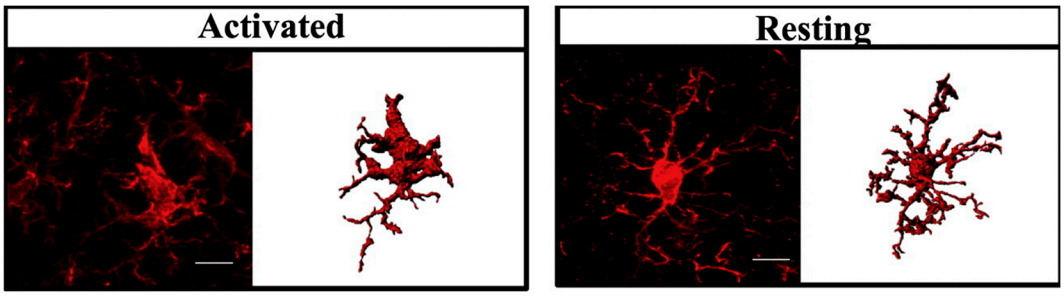

Figure 2. Taurine reverted the structural alterations of activated microglia cells to the basal state. Confocal micrographs immunostained for the ionized calcium-binding adaptor molecule 1 (Iba1) and 3D reconstruction of microglia in activated (**left**) and resting state (**right**). Reproduced from Gebara E, Udry F, Sultan S, & Toni N. Taurine increases hippocampal neurogenesis in aging mice. Stem cell research. 2015; 14 (3), 369–379 (Ref. [62]). This figure is reproduced from an open access article distributed under the terms of the Creative Commons CC-BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

As microglia activation was demonstrated to be reversed by taurine in the animal model, we hypothesize that this amino acid could revert some of the neurodegenerative processes in children with severe ASD.

6. Taurine Induces Autophagy

Lysosomes use an evolutionary preserved mechanism called autophagy to destroy extra or damaged cell organelles and proteins. When Ashford and Porter discovered in 1962 that cells could devour themselves, they made the first observation of the autophagy process [63]. Autophagy is a critical developmental mechanism that occurs during synaptic pruning. Both in human and animal models, deficiencies in autophagy have been linked to neurodevelopmental disorders such as ASD. Repeated early exposure to aluminum-containing vaccines during crucial immunological and neurological system development is among the environmental factors linked to ASD (for reviews, see [64–68]). Microglia, the main resident immune cells of the brain and spinal cord, constitute up to 15% of all CNS cells [69]. These "macrophage-like" cells are vital for maintaining brain homeostasis because they carry out key activities such as synaptic pruning and neurogenesis [69,70]. In reaction to harm brought on by either endogenous or exogenous stimuli, microglia can become activated [71].

The first report that aluminum from vaccines activated microglia cells in the animal model was delivered by Crépeaux and colleagues [72]. Subsequent work confirmed the presence of aluminum inside microglia in the brains of patients who died from ASD [66]. Furthermore, elevated levels of aluminum were found in human brain tissue samples of patients with sporadic Alzheimer's disease, familial Alzheimer's disease, ASD, and multiple sclerosis [73]. According to recent studies, autophagy exerts a significant role in maintaining brain homeostasis by controlling the activation degree of microglia [69,71]. Of note, it has been shown that autophagy is substantially dysfunctional in ASD brains and does not change normally over development, suggesting that both autophagy dysregulation and ASD etiology are involved (for reviews, see [64–68]).

Furthermore, it has been established that autophagy is a critical intracellular mechanism for macrophage and microglial polarization [74]. The promotion of M2 phenotypic polarization in microglia may result in a neuro-protective state as a result of increased microglial autophagy [75]. In conclusion, aluminum from vaccines (and other environmental/genetic factors) impairs autophagy by inducing excessive microglia activation, thus

affecting normal neurodevelopment. In this regard, it is important to consider taurine as a potential therapeutic molecule for ASD as evidence has been provided that taurine induces autophagy (Figure 3) and reverts the M1 to the M2 polarization state [48].

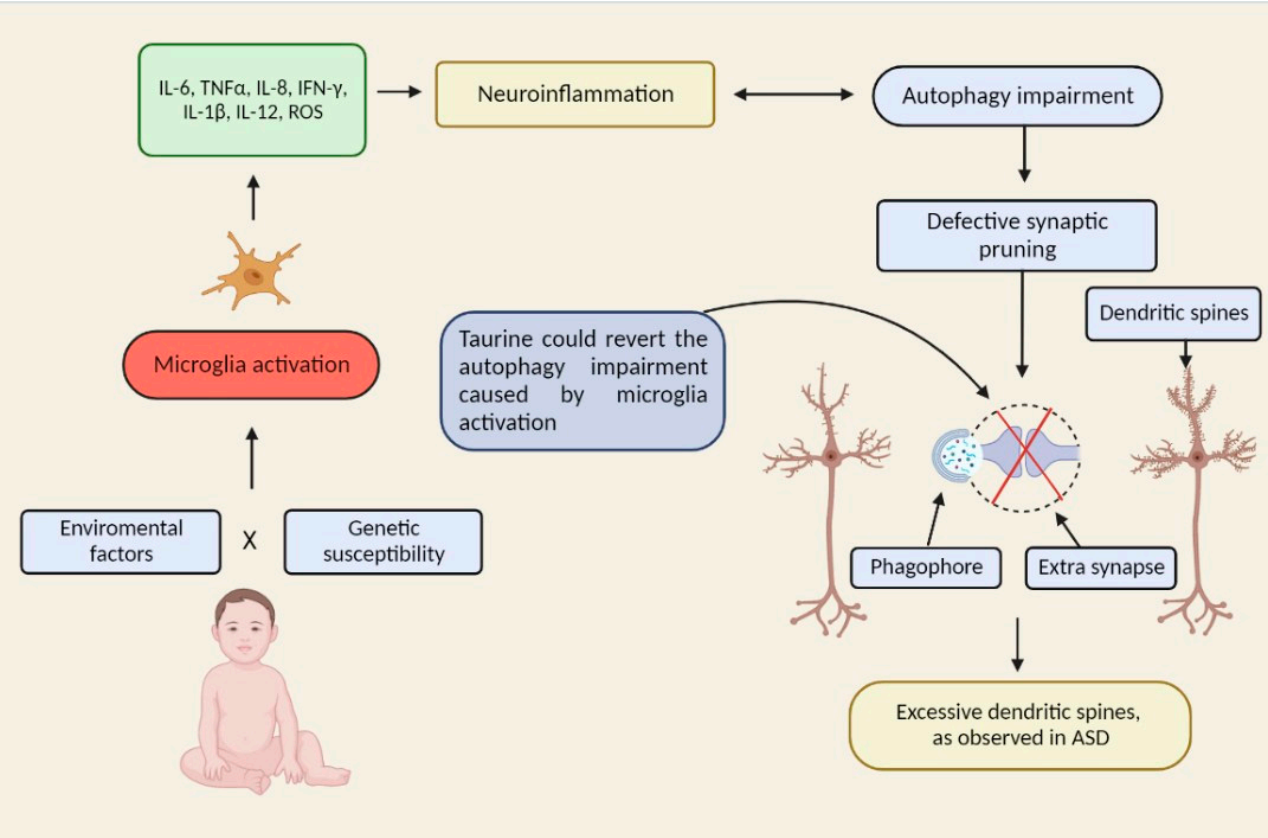

Figure 3. Autism spectrum disorder (ASD) results from exposure to environmental factors + genetic susceptibility. After that exposure, microglia cells in the brain become activated and induce a neuroinflammatory state characterized by autophagy impairment, which consists of defective synaptic pruning (the extra synapses are not removed by microglia cells, so the neurons from ASD brains have an excessive amount of dendritic spines. The "intense world syndrome," which describes the autistic brain as hyper-reactive with a hyper-connectivity of local neural circuits, is similar to this phenotype. Due to a greater number of synaptic connections and increased spine density, such complex connections are characterized by heightened neuronal information processing and storage inside the brain microcircuits (for review see [68]). Modified with permission from Angrand, L.; Masson, J.-D.; Rubio-Casillas, A.; Nosten-Bertrand, M.; Crépeaux, G. Inflammation and Autophagy: A Convergent Point between Autism Spectrum Disorder (ASD)-Related Genetic and Environmental Factors: Focus on Aluminum Adjuvants. Toxics 2022, 10, 518. https://doi.org/10.3390/toxics10090518 [68]. Created with BioRender https://biorender.com/ (acceded on 5 December 2022). This figure is reproduced from an open access article distributed under the terms of the Creative Commons CC-BY license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

7. Taurine Promotes Neurogenesis

Microglia cells are easily stimulated due to damage or immune stress [76]. Nitric oxide (NO), TNF-α, IL-1β, and Reactive Oxygen Species (ROS) are among the inflammatory substances secreted by activated microglia [77]. Furthermore, neuronal degeneration has been linked to the synthesis and accumulation of these substances [24,78–80], and it has been observed that microglia over-activation causes apoptosis [81]. One study, for example, collected autistic brain cells obtained from a brain tissue bank to examine their cellular

and molecular alterations [82]. Three important brain sections, the hippocampus, the cerebellum, and the frontal cortex, were examined in six cases of autistic brains and six cases of non-autistic brains from deceased children aged 6 to 16. This analysis revealed that the three regions had a significant elevation in ER (endoplasmic reticulum) stress, as evidenced by the engagement of ER stress signals, such as serine/threonine-protein kinase/endoribonuclease IRE1, cyclic AMP-dependent transcription factor ATF-6-α (ATF6), and eukaryotic translation initiation factor 2-alpha kinase 3 (EIF2AK3, also known as RKR-like endoplasmic reticulum kinase (PERK)) [82]. It was also discovered that apoptosis rose in the three described areas, as evidenced by enhanced caspase 8 and PARP (poly (ADP-ribose) polymerase) breakdown [82].

We can deduct from this information that managing excessive oxidative stress is critical for preventing neuron death in the brains of some children who suffer from the most severe forms of ASD. Taurine has been demonstrated to be an essential component in the maturation of brain tissues [83] since its concentration is three to four times more elevated in the growing and newborn brains of mice than in adults [84]. Studies in monkeys that were fed with taurine-deficient dietary formulae revealed a significant deficiency in the cortical layer arrangement in the visual cortex [83]. Cats born from mothers with taurine deficiency had a reduced brain mass and altered cerebellum and visual cortex structure [85,86]. In taurine-deficient kittens, the number of pyramidal cells was diminished, and the neurons had poor ramification patterns [85,86]. Such findings highlight the significance of this amino acid for developing brains. Taurine has also been shown to promote or reestablish cellular division in neurons from human fetuses [87] and to affect neurotransmission [88]. Overall, these observations indicate that taurine is indispensable for adequate brain cell multiplication, growth, and specialization [89].

In this line, it was discovered that taurine significantly boosted the quantity of neuron progenitor cells (NPCs) collected from the hippocampal region of the aging mouse brain, and the increase in the NPCs stimulated by taurine was one of the greatest documented for any other molecule or situation in adult brain NPCs [90], far higher than that stimulated by melatonin, dopamine, or neuropeptide Y [91–93]. Furthermore, a seminal work demonstrated that taurine significantly enhances cell counts in vitro and neuron formation from fetal human NPCs [94].

Another study found that taurine stimulated NPC multiplication in the dentate gyri of developing brains, cultivated hippocampus progenitor cells, and hippocampus segments taken from mice brains. Taurine was also found to increase the generation of new synapses, which was a significant discovery [89]. Although such an increase persists during the lifetime in healthy people, a burst of synapsis production takes place throughout the initial brain maturation, termed "exuberant synaptogenesis" [95].

8. Conclusions

As mentioned in the introduction, the CNS contains a specialized population of macrophage-like cells known as microglia. Considered immune sentinels that are capable of orchestrating a potent inflammatory response, microglia can perform a variety of functions [18]. One such important microglia function is related to phagocytic action during neuronal/synaptic development (most likely represented by the elimination of repetitive neurons and synapses) [19]. Microglial activation or malfunction can have a significant impact on neuron maturation, leading to neurodevelopmental dysfunction, such as ASD [17]. Microglia, like macrophages, respond to CNS injuries by adopting distinct activated profiles [20].

When microglial cells are activated, they undergo phenotypical changes, that is, a change from the M2 to the M1 phenotype, known as M1 polarization [17]. M1 polarization has been involved in a variety of nervous system abnormalities, such as multiple sclerosis, Alzheimer's disease [96], and ASD [42]. According to recent studies, increasing the M2 phenotype may improve cognitive performance [97]. It was found that transplanting natural IL-4 functional T cells into IL-4 knockout mice improves their behavior while transplanting

M2-activated macrophages enhances mental performance in immunologically defective mice [98,99]. These findings reveal that M1 polarization has negative impacts on brain performance, whereas M2 polarization can counteract some of those consequences [14]. Results from these animal studies are encouraging, and we suggest that there may be a therapeutic opportunity to reprogram the metabolism of M1 macrophages that are over-activated in the ASD brain.

Irrespective of the origin, some children with ASD may have a severe inflammatory process in their brains, which interferes with appropriate neuronal maturation and leads to neuronal death [82]. As taurine promotes neurogenesis, synaptogenesis, and also reprograms the macrophage M1 polarization state to the M2 phenotype, we hypothesize that taurine administration could be useful to decrease neuroinflammation and neuron apoptosis, thus improving cognitive function. Regrettably, existing therapeutic interventions for ASD only treat the symptoms that come along with this disorder; they do not modify disease progression and do not produce adequate symptomatic relief for the main symptoms [100,101]. The concomitant mental symptomatology of some ASD patients involves a lack of concentration, stress, aggressiveness, restlessness, and self-damage, in conjunction with sensory, sleeping, and gastrointestinal disorders [102,103].

To date, there are only two specific drugs for ASD authorized by the US Food and Drug Administration (FDA) for alleviating psychological symptomatology: risperidone and aripiprazole [104,105]. Unfortunately, there are not many clinically effective treatments for the iconic ASD symptomatology [106,107].

Since a pioneering study in the 1980s demonstrated that taurine blocked aggressive behavior in mice [108], we suggest that taurine could also help treat irritability and aggressive conduct in some children with ASD, besides the other aforementioned important effects. Taurine is cheap, readily available, and does not produce severe side effects, making it an excellent candidate for ASD treatment. Although taurine has been used in clinical treatments, in 2015, a study in rats assessed for the first time its potential to protect the brain against oxidative damage caused by aluminum [109]. When compared to the control group, aluminum consumption significantly increased malondialdehyde (MDA) levels, while reducing the activities of superoxide dismutase, glutathione peroxidase (GSH-Px), Na+-K+-ATPase, and Mg2+-ATPase in the brain. The MDA content was substantially reduced after taurine supplementation, while the activities of the aforementioned enzymes were enhanced when the highest dose was used (800 mg/kg/day). The authors concluded that taurine administration can increase the activity of antioxidant enzymes and ATPase, which may be protective against aluminum-induced neurotoxicity [109]. Taurine deficiency is linked to a wide spectrum of clinical disorders, according to mounting evidence. Taurine is without a doubt one of the most important molecules in the body, despite being one of the few amino acids not employed in protein synthesis [110].

To investigate the probable function of taurine in ASD, serum was taken from 66 children with ASD (males: 45; females: 21, ages 1.5 to 11.5 years, average age, 5.2 $\pm$1.6). Children with ASD did not significantly differ in taurine concentration from their siblings who were not impacted by the disease. However, 21 out of 66 ASD patients exhibited low serum taurine levels (<106 M). According to this research, taurine may serve as a reliable biomarker in a subpopulation of ASD children [111].

Of note, it has been demonstrated that aluminum exposure (281.4 mg/kg/day for 1 month) in rats, led to considerable decreases in the levels of taurine and GABA (gamma-aminobutyric acid) in the rat brain [110]. Taurine and GABA are inhibitory neurotransmitters, thus if neural inhibition is impaired by aluminum and other environmental factors, the glutamate pathway is hyperactivated through the mammalian target of rapamycin (mTOR) signaling, which results in impaired autophagy (characterized by an increased dendritic spine density with reduced developmental spine pruning). Overactive mTOR signaling may produce an excess of synaptic protein synthesis, which could indicate a common mechanism underlying ASD [112]. The mTOR pathway is one of the widely recognized regulators of autophagy [113]. mTOR is a serine/threonine protein kinase

that consists of two subunits, mTORC1 and mTORC2. By phosphorylating ULK1 and ATG13, mTORC1 is an important negative regulator of autophagy that prevents this activity. When mTORC1 phosphorylates ULK1, its catalytic activity is suppressed, which prevents the start of autophagy [114]. In this regard, it is important to mention that taurine inhibits Akt/mTOR signaling and activates autophagy [115]. Interestingly, it has been demonstrated that the effects of mTOR blocking included a reduction in lesion size, a sharp decline in the production of cytokines and chemokines that promote inflammation, and a decrease in the M1-type microglia number [116].

Excessive glutamate release through the mTOR pathway can negatively impact the autophagy process [114]. In this regard, it is important to mention that astrocytes are responsible for the clearance and transport of glutamate, which is possible due to the presence of glutamate transport proteins (GLAST) and glutamate transporter 1 (GLT-1) on astrocytic membranes. Abnormalities of astroglia cells regarding glutamate metabolism may lead to behavioral impairments; for a review see [117].

Finally, in a recent work, taurine was administered to lipopolysaccharide (LPS)-treated mice and microglial (BV-2) cells. Taurine inhibited the LPS-induced increase in lysine demethylase 3a (KDM3a), a promoter of inflammation and microglia activation, improved the sociability of LPS-treated mice, inhibited microglia activation in the hippocampus, and reduced generation of brain inflammatory factors, such as interleukin-6, tumor necrosis factor-α, inducible nitric oxide synthase, and cyclooxygenase-2 [118].

Based on these compelling data, we hypothesize that oral taurine administration could restore levels of this amino acid to its basal state, thus restoring normal autophagy function. As taurine also promotes neurogenesis and synaptogenesis, it might improve cognitive function in severe cases by dampening the neurodegenerative process caused by apoptosis. All these neuro-protective effects lead us to propose taurine as an effective treatment for ASD. Information regarding our recommended therapeutic strategy can be found in Appendix A. Clinical trials should be performed to test the validity of our hypothesis.

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Appendix A

Recommended Therapeutic Strategy

Experimental research showed that serum taurine concentrations (<106 µM) from 21 (10 females and 11 males) out of 66 children with ASD were remarkably lower, compared to the average taurine concentrations from their unaffected brothers and sisters (142.6 $\pm$ 10.4 and 150.8 $\pm$ 8.4 µM), leading the authors to suggest that taurine may be a valid biomarker in a subgroup of ASD patients [111]. Thus, low serum taurine levels could be used as a diagnostic tool and may further justify the therapeutic strategy we are recommending. Taurine treatment should be initiated in those ASD patients with low serum taurine concentrations.

Taurine treatment has been the subject of more than 30 peer-reviewed, human clinical experiments. Overall, the evidence indicates that supplementary taurine is rather safe [119].

There were no significant side effects recorded in any of the 30 trials analyzed, with the exception of some minor intestinal problems described in one study [120]. In the complete lack of a consistent trend of deleterious consequences in humans in reaction to oral route taurine, the Observed Safe Level (OSL) for taurine supplementation intakes in adults has been suggested to be up to 3 g per day [119].

In teenage cystic fibrosis sufferers, the lengthiest experimental period was 12 months at a concentration range between 500 and 1500 mg/day [121]. The median age of the patients in that research was 13.8 years, and they were given 30 mg/kg of body weight daily with no documented negative effects. To make therapy easier for children with ASD, we recommend giving them 30 mg/kg/day in a single dose. This concentration has been reported to be safe, and it is by far lower than the Observed Safe Level (OSL) of 3 g per day [119]. If no significant results are seen in the medium term, we suggest the concentration could be increased to 60 mg/kg/day.

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