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 immunocytochemical 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 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 the 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, neuronal death, and improving cognitive functions. Therefore, we think that taurine can serve as an important lead for the development of novel drugs for the ASD treatment.

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

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] were dedicated to finding 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 to-

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ward 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 the autistic behavioral alterations [15,16], and convincing research evidence indicates that microglial stimulation or disturbance can have a significant impact on the neural development, leading to the disorders in neuronal growth, such as ASD [17]. Basic research continues to be done to identify the causes that promote the development of ASD. However, most of this research is oriented more to the search for the causes of the disease than to the development of the effective medicines. As a result, children with ASD still do not have specific treatments capable of stopping the progressive neurodegeneration that some of they are affected with. This work provides the scientific rationale for the potential therapeutic utilization of taurine for the patients with ASD.

2. Microglial Activation in ASD

The central nervous system (CNS) contains a specialized population of macrophage-like cells known as microglia. Being considered as immune sentinels that are capable of orchestrating a potent inflammatory response, microglia can perform a variety of activities at various periods of life, both in normal and pathological conditions [18]. Microglia have a multitude of roles throughout CNS maturation, such as [19]:

- Phagocytic action during neuronal/synaptic development (most likely represented by the elimination of repetitive neurons and synapses);
- Neuron maturation is impacted by cytokines, neuro-hormones, and factors that promote their growth;
- Cell waste discharge enabling plasticity and synaptogenesis, and
- Stem cell growth control.

Appealing scientific proof implies that microglial activation or malfunction can have a significant impact on neuron maturation, leading to the neurodevelopmental dysfunction, such as ASD [17]. Microglia, like macrophages, respond to the 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 enhance 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 [20-22].

3. M1 polarization in ASD

Classically activated M1 macrophages are known to mediate excessive inflammatory responses, cytotoxicity, and tissue damage. They mediate host 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 the 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

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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 exert an important contribution to the pathophysiology of ASD in youngsters, according to the research [37]. In the brains of kids with ASD, immunohistochemistry indicated higher amounts of microglial cells in the parenchyma, 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 kids 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 the ASD diagnostics. In cultivated M1 and M2 macrophages obtained from the 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 such 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 the laboratory settings [21].

M1 macrophage, which is stimulated by TNF-α or IFN-γ stimulus, exhibits a significant increase in the glycolytic metabolism to generate ATP for phagocytic and microbicidal activities, whereas sustaining a pause in the mitochondrial tricarboxylic acid cycle (TCA cycle). 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].

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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 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 M1 macrophage power metabolism by preserving an elevated number of mitochondria that prevents 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 youngsters with ASD. Since taurine administration was shown to inhibit the release of these cytokines, one can imply 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 the sulfur amino acids, such as methionine and cysteine, and which is not employed in the protein biosynthesis. The enzyme cysteine sulfinic acid decarboxylase (CSD) synthesizes it from cysteine and methionine in the kidney, liver, and nerve cells, specifically in glia 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 [50,51,59,60,61] [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].

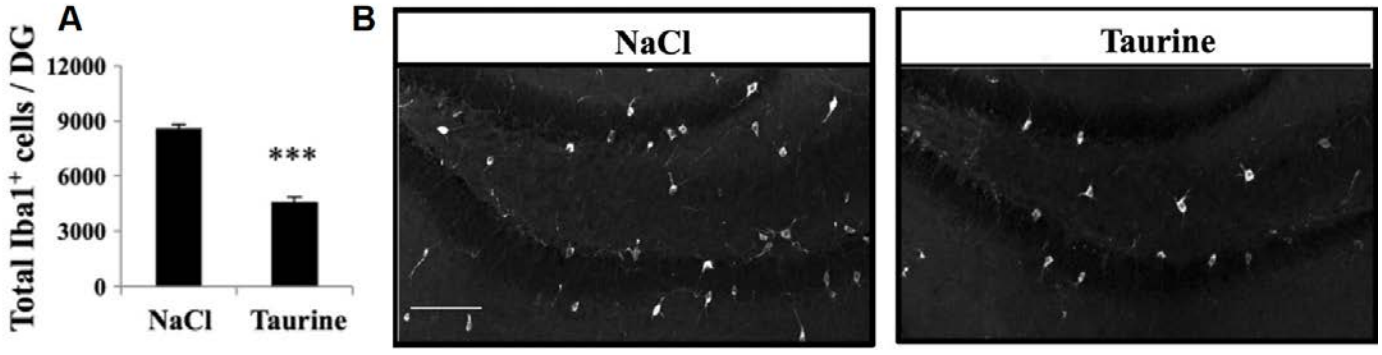

Figure 1. Taurine reduced the number of microglia and indicators of microglia activation. A) Histogram displaying the total number of cells in the dentate gyrus of the hippocampus. B) Confocal micrographs of the hippocampal sections immunostained for MHC-II (major histocompatibility complex II molecules). Reproduced with permission from Gebara E, Udry F, Sultan S, & Toni N. Taurine increases hippocampal neurogenesis in aging mice. Stem cell research. 2015; **14** (3), 369–379 [62].

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Microglia undergo structural alterations as a consequence of the 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 territorial projection area, and increased the number of microglia dendrites; these structural variations are associated with a lowered stimulated state of microglia [62].

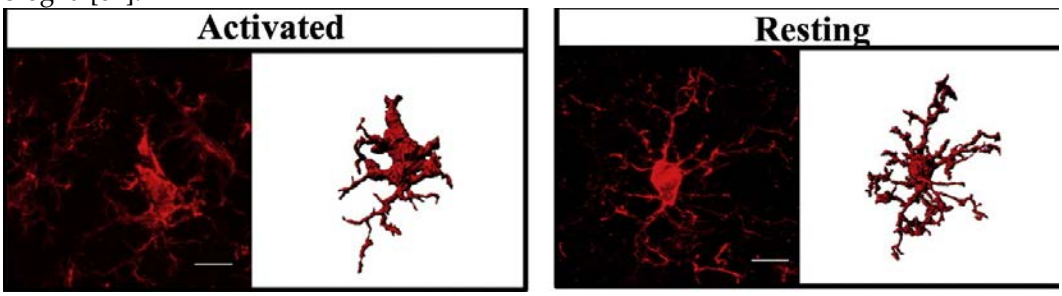

Figure. 2. Taurine reverted the structural alterations of activated microglia cells to the basal state. Confocal micrographs immunostained for the ionized calcium binding adaptor molecule 1 (Iba1) and 3D reconstruction of microglia in activated (left) and resting state (right). The Creative Commons CC-BY license governs the usage of this image, which allows for free use, sharing, and copying in every format only when the original project is correctly acknowledged. Reproduced with permission from Gebara E, Udry F, Sultan S, & Toni N. Taurine increases hippocampal neurogenesis in aging mice. Stem cell research. 2015; **14** (3), 369–379 [62].

As microglia activation was demonstrated to be reversed by taurine in the animal model, we hypothesize this aminoacid could inhibit the apoptotic death of microglia and other neurodegenerative processes in children with ASD if administered when the first symptoms appear.

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 like 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 the ASD brains and does not change normally over development, suggesting that both autophagy dysregulation and ASD etiology are involved (for reviews, see [64-68]).

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Furthermore, it has been established that autophagy is a critical intracellular mechanism for the macrophage and microglial polarization [74]. The promotion of M2 phenotypic polarization in microglia may result in a neuroprotective state as a result of increased microglial autophagy [75]. In conclusion, aluminum from vaccines 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 and reverts the M1 to the M2 polarization state [48].

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 kids aged 6 to 16. This analysis revealed that the three regions had a significant elevation in the 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 kids who suffer from the most severe forms of ASD. Taurine has been demonstrated to be an essential component in the maturation of the brain tissues [83], since its concentration is three to four times more elevated in the growing and newborn brain mice than in the adults [84]. Studies in monkeys that were fed with the taurine-deficient dietary formulae revealed a significant deficiency in the cortical layer arrangement in the visual cortex [83]. Cats born from moms with a 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 NPCs multiplication in the dentate gyri of the developing brains and 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

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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 stimulated 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 kids with ASD 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 ASD iconic symptomatology [106,107].

Since a pioneering study in the 80s demonstrated that taurine blocked aggressive behavior in mice [108], we suggest that taurine could also help treating the 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 the 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]. 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 GABA (Gamma-aminobutyric acid) and taurine in the rat brain [110]. GABA and taurine are inhibitory neurotransmitters, thus if neural inhibition is impaired by aluminum, the glutamate pathway is hyperactivated through the 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 [111].

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Appendix A

Recommended therapeutic strategy

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 [112]. There were no significant side effects recorded in any of the 30 trials analyzed, with the exception for some minor intestinal problems described in one study [113]. 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 grams per day [112].

In the teenage cystic fibrosis sufferers, the lengthiest experimental period was 12 months at a concentration range between 500–1500 mg/day [114]. 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 NOAEL (No Observable Adverse Effect Level) of 6 grams per day [109]. If no significant results are seen in the medium term, we suggest the concentration could be increased to 60 mg/kg/day. Treatment should be started as soon as the first symptoms are detected and should be closely evaluated by a pediatrician. Clinical trials should be performed to test the validity of our hypothesis.

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