Does infectious fever relieve autistic behavior by releasing glutamine from skeletal muscles as provisional fuel?

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A B S T R A C T

First reported formally in 1980, the frequent ability of infectious fever to relieve autistic behavior, often dramatically (and rarely aggravate), has long tantalized parents, practitioners, and researchers – yet its physiology and biochemistry have never been investigated, to judge from the literature. Fever is a complex interplay of immune, metabolic, and stress responses, yet its benefit in autistic disorders (ASD) may derive largely from a single response – release of the amino acid glutamine from skeletal muscles as provisional fuel. This proposal is based on evidence of low blood and brain glutamine in ASD children and adults, notable lack of autistic behavior in children with high brain glutamine from urea cycle disorders, and other events that elicit dramatic improvements – fasting, panic, pain, and the corticosteroid prednisone – that release or synthesize glutamine. Glutamine released from muscles is metabolized by the intestines like ingested glutamine. If glutamine released by fever rarely aggravates autistic behavior, why would supplemental glutamine?

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Introduction

[Children in this cohort [urea cycle disorders] show other behavioral/emotional strengths, including a minimal percentage with previous diagnoses of Autism spectrum disorders, mood disorders, and other psychiatric disorders. Krivitzky et al. 2009 [1].]  

High concentrations of ammonia in the blood of children with autistic disorders (ASD) were first detected in the 1980s [2]. Filipek et al. found plasma ammonia high in a majority of 100 autistic children [3]. Wakefield et al. proposed that bacteria in their diseased intestines generate more ammonia than their impaired liver can clear, which reaches the brain: “Following passive diffusion across the [intestinal] mucosa, failure by the diseased liver to effect what should, under normal circumstances, be a high first-pass clearance, leads to excessive ammonia levels in the brain.” [4] Bradstreet et al. noted that high blood ammonia is more toxic to children than adults [5]. Wang et al. recently reported high levels of fecal ammonia in ASD children [6].

Most ammonia is generated by bacteria digesting proteins in the large intestine, and decomposing the amino acid glutamine in the small intestine [7]. The liver uses the amino acid arginine to detoxify blood ammonia to urea, excreted in urine [8]. The brain lacks enzymes for this urea cycle, and is the organ most affected when the liver cannot clear blood ammonia rapidly (hepatic encephalopathy). Ammonia that reaches the brain is trapped by astrocytes combining it with the excitatory transmitter glutamate to form glutamine, with no transmitter activity but much osmotic activity. Brusilow et al. concluded that the primary pathology of ammonia in the brain is reversible astrocyte swelling from glutamate and its water [9]. Astrocytes also detoxify ammonia with α-ketoglutarate. Pangborn: “Ammonia grabs alpha-ketoglutarate, especially in the brain … where that’s the natural ammonia detox route. Ammonia plus alpha-ketoglutarate becomes glutamate.” [2] α-Ketoglutarate is also a key intermediate in the citric acid cycle that generates adenosine triphosphate (ATP) [10], thus depletion by ammonia reduces brain energy.

Albrecht and Jones concluded that acute ammonia toxicity releases glutamate at brain synapses, inducing excitation; chronic ammonia accumulation downregulates glutamate receptors and releases gamma aminobutyric acid (GABA), inducing inhibition [11]. Chronic ammonia accumulation also shifts brain metabolism and blood flow from cortical to subcortical structures [12]. Hindfelt noted that an early manifestation of hepatic encephalopathy is a “frontal lobe syndrome” – loss of cortical ‘executive’ functions [13]. Brain metabolism slows in early stages of hyperammonemia [14].

Children with inborn urea cycle disorders (UCD) cannot detoxify enough ammonia in the liver, inducing plasma ammonia concentrations 5×– greater than in liver failure [15], high brain glutamine, astrocyte swelling and intracranial pressure, and impaired cognition. Yet children with UCD rarely show autistic behavior [1,16,17]. One explanation might be that they detoxify more free brain ammonia than ASD children, but Felipo and Butterworth noted that glutamine synthetase, the astrocyte enzyme that neutralizes ammonia to glutamine, normally functions at near-maximum

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capacity [12]—implying UCD children have high brain glutamine and ammonia. If high brain ammonia doesn't provoke autistic behavior in UCD children, why would it do so in ASD children? One obvious explanation is that ASD children are not ‘protected’ by high brain glutamine.

**Glutamine in autistic disorders**

Because of the harmful systemic manifestations that would otherwise result, peripheral tissues such as skeletal muscle and the brain do not release significant amounts of free ammonia into the bloodstream. Instead they have developed methods of detoxifying this compound. Both of these organs synthesize and release glutamine which transports ammonia in a nontoxic form to the intestinal tract and the kidneys. Soubra 1987 [18].

Glutamine is normally the most abundant amino acid in blood [19], yet was low in serum, plasma, and platelets of ASD children [20–24]. Because glutamine is not thought to cross the blood–brain barrier significantly, the implications of low blood glutamine in these children are not recognized. Yet a sodium-dependent, concentration gradient-dependent transporter carries glutamine from blood into astrocytes [25]. Glutamine is an important alternative fuel in brain neurons and astrocytes, especially during hypoglycemia [26], and primary fuel in rapidly replicating cells, e.g. blood vessel endothelial cells, intestinal enterocytes, liver cells, lymphocytes, and tumors [19,27]. Two enzymes largely regulate intracellular glutamine metabolism. Glutaminase catalyzes hydrolysis of glutamine to glutamate and ammonia; glutamine synthetase catalyzes synthesis of glutamine from glutamate and ammonia. Releasing cells tend to be avid glutamine consumers, so have more glutaminase. Skeletal muscle, lung, and brain synthesize and release glutamine into blood, so have more glutamine synthetase [19]. Intestinal glial cells resembling astrocytes also synthesize glutamine [28].

Astrocytes take up the transmitter glutamate released at brain synapses (and via glutamine synthetase) neutralize it to glutamine, which they release to neurons to resynthesize glutamate (and GABA) and as fuel. Conversion of glutamate to glutamine requires ammonia – detoxifying both molecules. Persons with liver damage (e.g. cirrhosis) and children with urea cycle disorders cannot detoxify enough ammonia before it reaches the brain, inducing high brain ammonia and glutamine (hepatic encephalopathy) [12]. Wakefield et al., however, thought ASD children had high brain ammonia but low glutamine, because serum glutamine was low [20] and liver dysfunction impairs glutamate transporters [4]. Distinguishing brain glutamine from glutamate by magnetic resonance spectroscopy (MRS), usually requires an ultra-high (7 Tesla) field. DeVito et al. detected reduced concentrations of combined glutamate/glutamine in the cortex and cerebellum of autistic boys [29]. Bernardi et al. found less glutamine/glutamate in the right anterior cingulate cortex of high-functioning adults with ASD [30]. Page et al., however, found glutamate/glutamine elevated in the amygdala–hippocampal region of autistic adults, and normal in the parietal region [31].

Recent studies corroborate low blood and brain glutamine in ASD. Shimamura et al. detected high plasma glutamate and low glutamine in high-functioning autistic children [32]. Abu Shmais et al. found a high ratio of plasma glutamate to glutamine in ASD boys, and high plasma ammonia [33]. Horder et al. detected by MRS low concentrations of combined glutamate/glutamine in the basal ganglia (subcortex) of the brain in ASD adults that correlated well with impaired communication, language, planning, and other executive functions. Social and repetitive behaviors, however, did not correlate with basal ganglia glutamate/glutamine concentrations, nor did any symptoms correlate with glutamate/glutamine in the prefrontal or parietal cortex [34].

Conversion of glutamate to glutamine requires magnesium [26] and vitamin B6 [35] as cofactors – nutrients very effective against autistic behavior [36]. The effectiveness of risperidone (risperidal), which helped 54% of ASD persons (but aggravated 20%) [37,38] also suggests brain glutamine may be low. Risperidone is thought to suppress serotonin and dopamine activity at synapses, but also stimulates glutamate uptake by astrocytes and activity of glutamine synthetase [39]. The most compelling evidence for low brain glutamine in autistic disorders, however, must be the curious lack of autistic behavior in children with high brain glutamine from urea cycle disorders [1,16].

**Hypothesis: Does infectious fever relieve autistic behavior by releasing glutamine from skeletal muscles as provisional fuel? Is autistic behavior induced by lack of energy in the inhibitory cerebral cortex?**

Glutamine is metabolized similarly whether it enters the intestinal enterocyte from the lumen or from the bloodstream. Soubra 1991 [19].

Because children with urea cycle disorders rarely show autistic behavior [1,16], something must protect them, whether or not brain ammonia induces ASD. Two prominent explanations: UCD children have less extracellular brain glutamate, and more intracellular glutamine. Wakefield et al. thought glutamate accumulated in ASD brains at the expense of glutamine because ammonia released glutamate from neurons, but liver dysfunction impaired astrocyte glutamate transporters [4].

One intriguing clue that glutamine may be the protective factor is that infectious fever often relieves autistic behavior (often dramatically) and rarely aggravates [40–43]. Lack of appetite (anorexia) induced by fever rapidly depletes glycogen stores, releasing glutamine and other amino acids from skeletal muscles to blood as substrate for glucose [44]. Fever may relieve autistic behavior simply by increasing brain temperature, metabolism, and blood flow. Kiyatkin noted that fever elevates human brain temperature much more than ambient heat or stress, especially in children [45].

Fever accelerates brain metabolism by releasing epinephrine from the adrenal medulla [46,47], and shifting sodium ions from cerebrospinal fluid (CSF) into the brain, displacing calcium ions, thereby raising the set point for body temperature [48,49]. High temperature of fever breaks down muscle proteins to amino acids (catabolism) as metabolic fuel [44,50]. Sodium also carries glutamate into astrocytes for neutralization to glutamine, and activates the sodium pump, which requires conversion of glucose to lactate, a fuel neurons prefer [51]. Even so, low blood/brain glutamine in ASD children and adults, and notable lack of autistic behavior in UCD children with high brain glutamine, argue that glutamine is the decisive brain fuel in ASD. Corroborating this conclusion are other events that elicit notable improvements of autistic behavior – fasting [43,52], panic [53], severe pain [54], and the corticosteroid prednisone [43] – all of which release or synthesize glutamine.

ASD practitioners and patients report benefit from supplemental glutamine (largely gut healing) [55–57], but some practitioners are understandably wary of the ammonia that glutamine generates (which an impaired liver may not clear) or the glutamate [58]. The Autism Research Institute (ARI) recognized glutamine’s value to fuel the intestines, but warned against glutamine supplements when blood ammonia is high [59]. There is, however, a compelling argument that supplemental glutamine is safe in ASD. Some of the glutamine fever releases from muscles to blood may enter the brain directly via the concentration-dependent transporter [25].
Infectious fever relieves autistic behavior

Though there is practically no mention of the high fever/improved behavior phenomenon in the entire autism literature, every knowledgeable person – both parent and professional – I approached for information knew of it. Sullivan 1980 [40].

Anecdotal reports of fever’s benefit were published by Sullivan in Parents Speak, a column in the Journal of Autism and Developmental Disorders. Campbell described an outbreak of upper respiratory infection in a Bellevue Hospital nursery. Autistic children with fevers of 102–105 °F had longer attention spans and socialized with other children and adults. Most improvements subsided a few days after temperatures returned to normal. Caparulo and Cohen noted that stressful procedures like blood drawing also provoked brief dramatic remissions. Sullivan: “The change in the autistic child’s behavior [from fever] is more than quiet – it is a lucid calmness, as though he suddenly has a better understanding of what is happening around him.” [40]

Cotterill reported the phenomenon in 1985: “When autistics have a moderate fever, they invariably display dramatically more normal behavioural patterns, including a greater desire or ability to communicate. . . . The effect appears to reach a maximum for fevers in the range 1.5–2.5 °C [2.7–4.5 °F]” [41]. Brown described his personal observations in 1999 [42] and 2004: “The changes that occur in these autistic children are . . . dramatic, more like a metamorphosis in which the autistic child suddenly becomes almost normal. These children experience increased alertness, a decrease in social isolation and self-injurious behavior, an increase in verbal behavior, and an attempt to reach out and communicate with adults. And they don’t appear to be that sick.” [62]

These anecdotal reports inspired a prospective study by Curran et al., who compared the behavior of 30 ASD children during fevers greater than 100.4 °F (38 °C) against the behavior of 30 ASD children with no fever. More than half the parents already knew fever helped. During fever most parents observed less irritability, hyperactivity, repetitive acts, and inappropriate speech, which appeared to not depend on the severity of the illness, height of the fever, nor degree of lethargy [63]. Publication of this study provoked a spontaneous outpouring of parents’ reports of relief by fever in autism, ADHD, and other disorders. Surprisingly, three autistic children improved briefly from a sauna, steam room, or hot tub/bath. Zimmerman et al. concluded: “These reports suggest that methods for raising the core temperature may be as effective as fever in some individuals, and their rapid onset and transient nature might involve separate pathways from fever and immune responses.” [54] Informal parent surveys indicate fever helps 30–40% of ASD children [64].

Mehler and Purpura proposed that fever relieves autistic behavior by transiently normalizing the activities of the locus coeruleus (ceruleus) in the brainstem and its network of sympathetic nerves – the brain’s primary source of norepinephrine. These writers proposed that the locus coeruleus and its sympathetic network become dysregulated during development, partly by maternal stress, impairing their functions in thermoregulation and behavior. They noted that relief of autistic behavior by fever argues that “neural networks responsible for ASD, particularly in higher functioning patients, should be functionally intact.” [65]

A workshop on fever in autism [64] considered the effect of temperature to increase brain blood flow (consistently low in these children), but the usual lack of benefit of a hot tub or sauna argued against it [66]. The best explanation may be Kiyatkin’s observation that fever elevates human brain temperature much more than ambient heat: “In contrast [to fever], sauna or environmental warming affects brain temperature very little, especially in humans, because of sophisticated homeostatic mechanisms that maintain stability of body temperature.” [45]

How does fever accelerate brain metabolism?

Febrile illness is a natural stressor and a powerful stimulus of both the adrenal medulla and cortex. Keil et al. 2010 [47].

Because neurons require several orders of magnitude more metabolic energy than other cells (largely to restore resting potentials) the brain generates considerable heat [67]. Heat accelerates metabolic rate about 11% for each °C [68], so the hypothalamus regulates body and brain temperatures closely, normally 98.0–98.8 °F (36.6–37.1 °C) orally [46]. Temperature-regulating centers in the hypothalamus resemble thermostats in a home heating/cooling system. Hypothalamic ‘thermostats’ regulate and integrate the independent heating and cooling mechanisms of the body to stabilize temperature at the most appropriate set point. When bacterial or viral infection triggers the hypothalamus to raise body temperature to a new set point called fever, cooling mechanisms of vasodilation and sweating are suppressed as temperature rises. When fever plateaus at the new set point, skin blood flow returns to balance heat gain and loss, and the child feels neither cold nor hot [69]. When fever breaks (crisis or flush), skin blood vessels dilate abruptly and sweating is profuse [46]. Fever resembles the body’s response to cold – skin vessels constrict to conserve heat, and heat is generated by muscle contractions (shivering) and acceleration of metabolism [70]. Metabolic (nonshivering) thermogenesis during cold is stimulated by the sympathetic nervous system (SNS) transmitter norepinephrine [71]. Thermogenesis by fever may be largely stimulated by epinephrine from the adrenal medulla, which accelerates metabolism 5–10× more than norepinephrine [46].

Current views of fever implicate environmental pyrogens (fever-inducing agents) like bacteria triggering internal pyrogens (interleukins, prostaglandins) that directly stimulate heat
production. Tang and Kiyatkin: “It is unclear, however, whether this effect is triggered centrally (i.e., via brain metabolic activation and subsequent involvement of sympathetic mechanisms) or results from the direct action of endogenous pyrogens on peripheral heat-producing organs (i.e., liver, muscle, adipose tissue).” In addition, these substances affect multiple afferent pathways to the brain, thus transmitting a signal from the periphery and inducing metabolic brain activation.” [72] Roth argued that the heat of fever arises in the periphery, then is carried by blood to the body core and brain [73].

What is not disputed is that during fever the SNS accelerates metabolism. Sympathetic thermogenesis is most obvious in stimulation of newborn brown fat by norepinephrine, and mobilization of metabolic fuels (fatty acids, glucose from glycogen) by epinephrine. These catecholamines also accelerate metabolism during stress, generating an elevated temperature called stress fever. Stress fever is genuine fever – body temperature reset to a higher set point, stimulating heat conservation and production [74]. Why doesn’t stress fever relieve autistic behavior? Kiyatkin: “While data in humans are limited, it appears that fluctuations [in brain temperature] due to stress, environmental warming, etc. are relatively weak (up to 1.0–1.5 °C), but during fever this increase is much larger, especially in children.” [45]

Although catecholamines cannot cross an intact blood–brain barrier, some sympathetic brainstem neurons synthesize epinephrine [75]. Wortsman was convinced adrenal epinephrine during acute stress reaches the brain: “The plethora of central effects indicates access of the catecholamine to the CNS. This would be possible only in areas devoid of blood–brain barrier. There are two hypothalamic structures with these properties; one is the median eminence, and the other is the organum vasculosum laminae terminalis. The hypothalamus itself is a rich source for epinephrine, having the highest concentrations in the brain in most species.” [76]

**Fever increases brain sodium, displacing calcium (raising the set point), activating the sodium pump, and generating metabolic fuels**

Frosini studied the effects of ambient heat vs. fever to release the cryogenic free amino acids taurine and GABA and the cations sodium (Na+), potassium (K+), calcium (Ca2+), and magnesium (Mg2+) from blood to CNS [49]. Heat increased CSF calcium but fever increased it much more; only fever decreased CSF sodium. Frosini cited Myers and Veale’s proposal that fever raises the set point by shifting sodium ions into the posterior hypothalamus, displacing calcium ions [48].

Sodium ions entering cells from blood or extracellular fluid trigger the cell membrane sodium pump (Na+K+ATPase) to remove them. The sodium pump expels three sodium ions in exchange for two potassium ions, keeping extracellular sodium and intracellular potassium concentrations very high. Energy stored in the sodium gradient is slowly continuously released as sodium ions leak into cells from the pressure of their high external concentration and positive charge, and are carried into cells by membrane proteins that use the energy of the sodium gradient to transport other substances. Paemeleire reported that sodium cotransports glutamate released at brain synapses into astrocytes for neutralization to glutamine. Sodium influx activates the sodium pump, which requires glucose that astrocytes convert to lactate, a fuel neurons prefer [51]. Thus sodium entering astrocytes converts glutamate to glutamine, and sodium leaving via the sodium pump converts glucose to lactate.

Impairments of the sodium pump [77] greatly resemble pathologies detected or suspected in ASD. First, loss of sodium gradients reduces glutamate uptake by astrocytes. Wakefield et al. suspected brain glutamate was low in ASD because glutamate transporters were impaired [4]. Blaylock implicated extracellular glutamate in autistic hyperactivity [78]. Second, impairment of the sodium pump requires the sodium/calcium exchanger to remove sodium, accumulating intracellular calcium. Calcium impairs ATPase pumps by competing with magnesium ions required to hydrolyze ATP. Evidence of calcium accumulation in autistic brains has been reported [79]. Mg/B6 supplements have been most effective in ASD [36,80]. Third, ion gradients maintain cell volume. Astrocytes appear swollen in ASD [81], the osmolyte myoinositol is elevated [82], and osmolytes taurine and glutamine appear depleted [4,83].

**Fasting, panic, pain, and prednisone induce notable improvements – and release or synthesize glutamine**

Fluid diets before invasive medical procedures (e.g. colonoscopy) relieved autistic behavior noticeably [52]. Such fasting [43], like anorexia of fever, rapidly breaks down muscle proteins to glutamine and other amino acids as provisional fuel [44,84]. Stress too releases muscle glutamine [85] but plasma glutamine decreases, apparently because cells require more glutamine under stress than muscles provide [86]. This may explain why stress usually aggravates autistic behavior [87] but severe stress relieves it. Caparulo and Cohen thought sudden remissions during blood drawing were due to “increased attentional focusing that accompanies highly arousing, emotional states.” [40] Helt et al. noted multiple reports of seemingly-mute autistic children speaking in perceived emergencies (panic) [53]. The pain of a broken arm provoked brief communication [54]. Does severe stress induce severe stress fever, accelerating catabolism and glutamine release? The corticosteroid prednisone, which relieved autistic behavior dramatically [43], stimulates peripheral glutamine synthesis [88].

**Arginine, creatine, and taurine defend against ammonia**

The amino acid arginine detoxifies blood ammonia to urea in the liver [8]. Arginine is also the only substrate for the primary vasodilator nitric oxide. High levels of plasma nitrite in ASD children may reflect inducible nitric oxide responding to intestinal infection [89], depleting arginine as substrate for endothelial and neuronal nitric oxide, the brain’s primary vasodilators. Carrick and Carrick reported that oral arginine (4 g/day) calms unstable emotions and improves sociability dramatically in their adult son with ASD [90]. Arginine also spares glutamine. Wu et al.: “When dietary levels of arginine are high, intestinal synthesis of citrulline from glutamine and glutamate may be inhibited for sparing of glutamine and glutamate for other metabolic pathways.” [91]

Arginine (with amino acid glycine) is also required to synthesize the organic acid creatine in kidneys and liver [92]. Creatine and phosphocreatine shuttle ATP from mitochondria to cytosol and the cell membrane, thus are vital for energy metabolism, especially in muscles and brain [93]. Athletes ingest many grams of creatine daily to energize muscles; 1–2 grams a day improved alertness and cognition in persons with dementia or Alzheimer’s [94].

Inborn creatine deficiencies cause mental retardation, delay acquiring speech and language, seizures, and autism [93]. Minshew et al. detected by MRS decreased levels of brain phosphocreatine in high-functioning autistic adolescents and young men, suggesting “increased utilization… to maintain brain ATP levels, or a hypermetabolic energy state.” [95] Friedman et al. detected reduced brain creatine in ASD children 3–4 years old, and reduced N-acetyl-aspartate (NAA), a marker of neuronal density and metabolism [96]. A follow-up study found less creatine and phosphocreatine in gray matter of young ASD children [97]. Hardan et al. detected by MRS reduced levels of NAA, phosphocreatine, and creatine in the left thalamus of ASD children [98]. Kleinhans et al. found no significant differences in NAA or creatine/phosphocreatine in the
amygdalas of high-functioning ASD adults, but significant correlations between NAA and creatine and clinical ratings [99]. Ipser et al. detected by MRS age-related changes in NAA and creatine: ASD adults had more creatine in temporal lobes; ASD children had less creatine in occipital lobes [100]. Abu Shmais et al. detected high plasma creatine in ASD boys suggesting low brain creatine [33]. Although trials of creatine for autistic disorders have not been reported in the literature, Wöller reported online that creatine can be very effective in ASD children with low muscle tone, low metabolic energy, poor coordination, and difficulty with expressive language [101] (see Tests and remedies).

Creatine protects against ammonia in the developing brain, but is also reduced by ammonia, according to Braissant, who concluded that the ammonium ion (NH4+) “impairs the metabolism and transport of arginine in developing brain cells. . . . As arginine is a precursor, among other pathways, of creatine (Cr) synthesis, NH4+ exposure of the brain can lead to disturbances in cerebral energy and in particular in its Cr content. . . . The main function of the Cr/PcCr/CK [creatinine/phosphocreatine/creatine kinase] system in vertebrate cells is the regeneration of ATP as well as the cell buffering of high energy phosphates. In CNS specifically, the importance of Cr has been shown for the dendritic and axonal elongation (growth cone migration), the Na+-K+-ATPase activity, the release of various neurotransmitters, the maintenance of membrane potential, the Ca++ homeostasis and the restoration of ion gradients. In the mammalian brain, total levels of Cr and CK activity are well correlated, their highest levels being reached in brain cells described with high and fluctuating energy demands.” [92].

A recent study of nutrients and biomarkers in ASD children by Adams et al. reported: “The autism group had much lower levels of plasma ATP and . . . precursors to ATP” – which might also explain sulfate and methyldeficiency, they noted: “ATP is required in the kidney to resorb sulphate (recycling of sulphate is important because sulphate is poorly absorbed from the gut, and conversion from cysteine is slow). This study found a significant correlation of ATP with free and total plasma sulphate . . . suggesting that decreased ATP is a significant contributor to decreased sulphate levels in children with autism.” [35]

**Taurine vs. ammonia (and calcium)**

Acute ammonia challenge appears to release taurine more readily than any other amino acid studied. Albrecht & Schousboe 2005 [102].

The free (nonprotein) sulfur amino acid taurine has many critical functions throughout the body, notably brain osmolyte, inhibitory transmitter and croygen, intracellular calcium regulator, and magnesium complement [49,103–105]. The value of taurine to regulate calcium has been most studied in the heart. Huxtable and Chubb concluded stress shifts Ca2+ and taurine into heart muscle via β-adrenergic receptors stimulated by epinephrine: Ca2+ to strengthen contractions, taurine to distribute the Ca2+ in intracellular structures: “[T]his system provides a potentially important link between two agents that modulate calcium flux in the heart cell: β-adrenergic activation stimulates both calcium and taurine influx into the heart cell, and taurine modulates the pool size of free intracellular calcium.” [106] Bkaly et al. said: “Taurine has the ability to increase calcium availability for [heart] contraction and at the same time protect against calcium overload injury.” [107]

Albrecht and Schousboe noted that various environmental/pathophysiological insults evoke “massive release” of taurine from the CNS [102]. Fos and Wu found most taurine was released from the brain by ischemia, free radicals, metabolic poisons, excessive glutamate, and ammonia: “[T]aurine is a powerful agent in regulating and reducing the intracellular calcium level in neurons. After prolonged l-glutamate stimulation, neurons lose the ability to effectively regulate intracellular calcium. . . . Under these conditions, significant amounts of taurine (mM range) are released from the excited neuron. This extracellular taurine acts to slow the influx of calcium into the cytosol through both transmembrane ion transporters and intracellular storage pools.” [103]

Taurine also suppresses arginine vasopressin, a hypothalamic hormone the pituitary releases to retain water at the kidneys. Sensing low ion concentrations in extracellular fluid, specialized astrocytes (pituicytes) release taurine to inhibit Ca2+ fluxes into neurons that release vasopressin. Hussy et al. concluded that taurine depletion “abolishes the osmo-dependent inhibition of vasopressin release.” [108] Low blood sodium (hyponatremia) releases taurine and glutamine from brain cells to maintain cell volume [109]. Small organic solutes like taurine are valuable osmolytes because (unlike electrolytes) they don’t destabilize proteins or (usually) alter membrane potentials [110].

**Taurine in autistic disorders**

Pangborn found taurine was the amino acid most wasted or depleted in urine of ASD children [83]. Taurine appears most vulnerable to abbreviated breastfeeding [111], dietary deficiencies of its precursors methionine and cysteine [112], impaired synthesis from deficiency of bioactive B6 (pyridoxal phosphate) [83], and preemptory requirements for sulfate and glutathione. Mother’s milk is rich in taurine; cow’s milk is low after calves are weaned [111]. Many mothers of autistic children breastfed one week [113]. Schultz et al. found longer breastfeeding was associated with a decreased likelihood of developing autism [114] – yet many (but not all) infant formulas have been fortified with taurine since the mid-1980s [115]. The Autism Research Institute recommended 250–500 mg/day of taurine for children with ASD, up to 2 g/day for adults and adult-sized children [116].

**Low brain blood flow in autistic disorders**

Arginine depletion may also explain low cerebral blood flow (CBF) in ASD. Zilbovicius et al. detected reduced blood flow in the frontal cortex of autistic children 3–4 years old resembling blood flow in normal children half their age. Three years later, frontal perfusion was normal: “Since CBF patterns in children are related to maturational changes in brain function, these results indicate a delayed frontal maturation in childhood autism.” [117] Ohnishi et al. reported decreased regional cerebral blood flow (rCBF) in brain regions implicated in autism, and observed no region with increased rCBF [118]. Burrioni et al. found global CBF reduced in autistic children, though some regions had greater than normal flow. Left hemisphere flow was less than right hemisphere flow, although both were low [119]. Degirmenci et al. detected asymmetric hypoperfusion in ten autistic children (and their family members!) [120]. Gendry Mesesse et al. found blood flow low in the superior gyrus of the left temporal lobe: “The more severe the autistic syndrome, the more rCBF is low in this region, suggesting that left superior temporal hypoperfusion is related to autistic behavior severity.” [121] Herbert noted the lack of physiological explanations for brain hypoperfusion in ASD [122]. Is low brain blood flow secondary to low metabolism? Friedman et al. cited reports of decreased metabolism in the “frontal lobes, basal ganglia, putamen, insula, thalamus, parietal lobes, temporal lobes, superior temporal gyri, and calcarine cortex” of ASD children [96].

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Why is ammonia high in autistic disorders?

Wakefield et al. suspected intestinal bacteria in ASD children generate more ammonia than their impaired liver can clear [4]. Reports of regression into autism soon after a course of broad-spectrum oral antibiotics – usually to treat otitis media (middle ear infection) – led Sandler et al. to investigate intestinal bacteria in these children. Oral vancomycin (an antibiotic minimally absorbed) improved autistic behavior impressively short-term [123]. Finegold et al. subsequently found ASD children had significantly different species of intestinal bacteria than typical children [124]. Adams et al. noted: “Commonly used oral antibiotics eliminate almost all of the normal gut microbiota. . . . Loss of normal gut flora can result in the overgrowth of pathogenic flora, which can in turn cause constipation and other problems.” [125] Horvath and Perman found autistic regression between 12 and 18 months was associated with the onset of gastrointestinal symptoms [126].

Fallon found many autistic children under the age of three with otitis media treated with the antibiotic amoxicillin/clavulanate (Augmentin), which she thought might elevate blood ammonia [127]. Analyzing medical records, Niehus and Lord concluded that ASD children had more ear infections than typical children, and were treated with more antibiotics [128]. Gordon has contended [129]. Greenberg et al. noted the association of acute otitis media with the antibiotic amoxicillin/clavulanate was “the first therapeutic choice” for children in day care centers: “The development and spread of resistant organisms are facilitated in DCCs as a result of the following: (i) large numbers of children; (ii) frequent close person-to-person contact; and (iii) a wide use of antimicrobial medications. Intensive antimicrobial usage provides the selection pressure that favors the emergence of resistant organisms, while DCCs provide an ideal environment for transmission of these organisms.” [130].

Ball noted that Augmentin was launched in 1981 to treat “upper and lower respiratory tract infections, urinary tract infections, skin and soft tissue infections and obstetric, gynaecological and intra-abdominal infections.” [131] A year earlier, another medication now implicated in ASD became popular with parents, pediatricians, and hospitals – acetaminophen (paracetamol, Tylenol), the antipyretic/analgesic of choice after aspirin was mistakenly implicated in Reye's syndrome in 1980 [132,133]. Until about 1980, approximately 50–60% of autistic children were abnormal from birth, and 40–50% regressed into autism at about 18 months [83]. “Around 1980,” Pangborn observed, “all this began to change. The total frequency of occurrence doubled, doubled again, and by 1995 was approximately 10 times that of 1980. Furthermore, while the onset-at-birth type had increased 3 to 4 times, the onset-at-18-months type had skyrocketed to considerably more than 10 times its 1980 level.” Pangborn concluded that most of the autistic population now appeared to have “an acquired disease caused by something that we were not doing 20 years ago.” [83]

Discussion: Does ammonia induce autistic behavior? Is glutamine a safe remedy?

Autism is a particularly interesting and significant clinical syndrome for neuroscience, because it is defined by abnormalities in those abilities that most distinguish humans from animals, that is, social and nonsocial behavior, language, and cognition. Minshew et al. 1993 [95].

Parent report has confirmed reductions in adverse behaviors with fever. Despite the significance of this observation, it would be even more important if anecdotal reports of increased emotional contact and speech with fevers could be confirmed. Helt et al. 2008 [53].

[T]he social milestones that are delayed in autism arise out of the self-regulatory milestones relative to orientation/attention, self-soothing, and the emerging ability to regulate behavior and emotions in response to social cues. Silva & Schalock 2012 [134].

Accumulation of ammonia in brain results in a redistribution of cerebral blood flow and metabolism from cortical to sub-cortical structures.Felipo & Butterworth 2002 [12].

Eminent researchers independently conclude that children with autistic disorders lack brain energy:

I had thought of [autistic behavior] as low energy, not enough to fire things sufficiently. Herbert 2011 [135].

I have come to the conclusion that autism is caused by energy deficiency, the complex details being different in each child. I think the net result is that the hard wiring of the brain is held back and the child is more primitive than his chronological age. Lonsdale 2011 [136].

Energy deficiency in the brain can arise from lack of nutrients (hypoglycemia) or oxygen, lack of blood flow to supply nutrients and oxygen, or direct impairment of energy metabolism (e.g. by enzyme deficiency). Children with autistic disorders are often hypoglycemic, brain blood flow is consistently low, and a great variety of metabolic deficits have been detected or suspected, notably depletion of magnesium (required for energy metabolism), amino acids (brain fuel), catecholamines, and detoxicants. Curiously, however, each child with an autistic disorder often has a relatively unique assortment (‘subset’) of metabolic deficits, although autistic behavior is distinctive and readily recognized [137]. As Herbert put it: “How do. . . . so many different mechanisms induce behavior that looks the same?” [135] Herbert suggested some metabolic deficits may be contributing factors. Others may be collateral damage. Abu Shmais et al. pointed out that many deficits impair brain energy metabolism via a common pathway – impaired creatine metabolism, loss of intracellular ATP, Ca2+ accumulation, and formation of reactive oxygen species [33].

Energy deficiency in the brain may alter mood and behavior simply by reducing metabolism in the inhibitory cortex (executive dysfunction; frontal lobe syndrome; release phenomena). Impaired cortical metabolism may explain why “human” attributes are compromised (Minshew et al.), brain maturation is delayed (Zilbovicius et al.), self-regulatory behavior is delayed (Silva & Schalock), and these children appear “more primitive” (Lonsdale). Impaired cortical metabolism may also explain why fever stimulates awareness, speech, and relating in these children, often dramatically (Sullivan; Cotteril;Brown;Helt et al.).

But if fever relieves autistic behavior by accelerating brain metabolism, why do some improvements persist days after temperature returns to normal [40,43,66]? Does fever release a protective factor that lingers, or reduce a harmful factor that returns? One such harmful factor might be ammonia, because fever reduces appetite (anorexia), thus (presumably) digestion of protein. Despite the commendable simplicity of this explanation, fever increases blood ammonia because proteins break down faster at high temperatures [138].

Furthermore, children with high brain ammonia (and glutamine) from urea cycle disorders rarely show autistic behavior. This must be a ‘smoking gun’ – but what does it imply? If high brain ammonia doesn’t provoke autistic behavior in UCD children, why would it do so in ASD children? Do ASD children have more free
brain ammonia because less converts to glutamine? Yet their blood ammonia is much lower than in UCD. Alternatively, does more glutamine or less glutamate in UCD protect against ASD? If glutamine helps more than glutamate harms, does high brain glutamine prevent autistic behavior – or does low brain glutamine provoke it?

Glutamine deficiency in mitochondrial cultures impaired protein metabolism [139], challenging prevailing views that glutamine is nonessential or only conditionally essential. Glutamine "starvation" in critical illnesses impaired many proteins [140]. Yet glutamine deficiency disorders appear rare, probably because skeletal muscles and the liver (and brain) synthesize and release glutamine as well as consume it [18]. Wernerman noted that healthy humans produce 50–80 g of glutamine a day [141]. Glutamine depletion is most obvious in severe catabolic states like sepsis, injury, and chronic HIV infection [18,85]. This argues that high brain glutamine more likely protects against autistic behavior than low glutamineprovokes it. But not always. Groppman et al.: "Patients with partial urea cycle enzyme deficiencies who manifest with late-onset presentations may have less obvious features including chronic encephalopathy, autism, learning disorders, hyperactive and self-injurious behaviour, vomiting with changes in level of consciousness… and, in teens and adults, psychiatric symptoms including episodic psychosis, bipolar disorder and/or major depression." [14]

How might high brain glutamine in UCD protect against brain ammonia it doesn’t detoxify? Glutamine is substrate for glucose, also for citric acid cycle intermediates (e.g. α-ketoglutarate) that ammonia depletes [44,142]. Ammonia induces excitability, but also clouding of consciousness, a frontal lobe syndrome with loss of cortical oversight. When ammonia accumulates, brain metabolism and blood flow shift from cortical to subcortical structures. Thus glutamine may compensate brain ammonia by maintaining cortical metabolism. Glutamine also carries water; are autistic brains dehydrated? Still, high brain glutamine provokes its own encephalopathy – or does it? [14,60].

Shabert noted that the stress of infection or injury releases 3–4× normal amounts of glutamine from muscles [85]. A clinical biochemist pointed out that muscles don’t have that much free glutamine; most must come from breakdown of muscle protein [143]. Hammarqvist et al. drew a similar conclusion after a three-day fast [84]. Bergström et al. biopsied muscle tissue in healthy adults, precipitated out the proteins, then measured the remaining free amino acids: "The majority of the amino acids showed much higher concentration in intracellular water than in

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**Fig. 1.** Synopsis of the argument. Infectious fever often relieves autistic behavior (often dramatically) and rarely aggravates. The most salient aspect of fever is an increase in brain temperature far greater than the hypothalamus normally allows. CSF sodium displaces brain calcium, raising the temperature set point. Epinephrine from the adrenal medulla (and brain) releases fatty acids and glucose from glycogen as metabolic fuels, and accelerates metabolism 5–10× more than norepinephrine. High temperature breaks down muscle proteins to amino acids as substrate for glucose. Extracellular sodium also carries glutamate into astrocytes for neutralization to glutamine, an important substrate for glucose during hypoglycemia. Sodium influx activates the sodium pump, requiring conversion of glucose to lactate, a fuel neurons prefer. Fever also induces loss of appetite, releasing glutamine and other amino acids from muscles as provisional fuel. Blood glutamine is consistently low (brain glutamine often low) in ASD children and adults; children with high brain glutamine from urea cycle disorders rarely show autistic behavior. Supplemental glutamine heals the intestines (and improved autistic behavior) but some practitioners are wary of the ammonia/glutamate that glutamine forms in the intestines, often already high in these children. Glutamine released by fever, however, also forms ammonia/glutamate in the intestines. If glutamine released by fever rarely aggravates autistic behavior, why would supplemental glutamine?
plasma. The concentration gradient was especially high for taurine, glutamic acid, and glutamine. As skeletal muscle contains the largest pool of intracellular free amino acids it is of interest to estimate the size of this pool. For a normal man with a body weight of 70 kg and a muscle mass of 40% of the body weight, the total volume of intracellular muscle water is 18.2 liters and the total intracellular amino acid content in muscle is 86.5 g. Of this total pool of free amino acids the eight essential amino acids represent only 8.4%, whereas free glutamine constitutes 61%, glutamic acid 13.5%, and alanine 4.4%.” [144]

Sixty-one percent of 86.5 g of intramuscular free amino acids equals almost 53 g of free glutamine. If muscles normally produce most of 50–80 g of glutamine a day [141], they may release that much into blood. For fever to release 3–4× that much glutamine [85], extensive catabolism must occur. Can a child be given as much glutamine as fever provides? Perhaps only gradually, via accumulation and synthesis in muscles, liver, and brain. Creatine builds muscles that synthesize and store glutamine; arginine spares glutamine and makes creatine. Some glutamine that fever releases from muscles to blood may enter the brain directly. Much more glutamine is presumably taken up by the intestines, where much forms ammonia and glutamate. If fever increasing intestinal glutamine rarely aggravates autistic behavior, why would supplemental glutamine? (see Fig. 1: Synopsis of the argument; Table 1: Best evidence).

Why don’t ASD children convert more brain ammonia + glutamate to glutamine? Wakefield et al. noted that liver dysfunction impairs astrocyte glutamate transporters [4]. Acute high blood ammonia directly impairs glutamate transporters (although chronic high ammonia may not) [12]. Low blood sodium and impairment of the sodium pump impair glutamate uptake [51,77]. Many known deficits in ASD impair the sodium pump: ammonia, depletion of magnesium, creatine, and ATP, hypoglycemia, and low brain blood flow [14,145]—yet overactivity has been detected [79]. Although most practitioners reported that hypotension is rare in ASD, a few found it as common as salt cravings [146].

Detecting high plasma ammonia and high GABA in blood and urine of an autistic boy, Cohen noted plasma GABA is consistently high when plasma ammonia is high [147]. Dhossche et al. found high plasma GABA in ASD children 5–15 years old [148]. GABA is the primary inhibitory transmitter in the CNS as well as primary cryogen. Frosini found that heat stress in rabbits increased cryogens taurine and GABA in CSF; fever increased CSF taurine but decreased GABA. Frosini suggested GABA might fail to allow elevation of the set point [49]. Burrus recently proposed that ammonia generated by the intestinal yeast Candida albicans forms a substance that acts like GABA in ASD brains [149].

Wakefield et al. suspected intestinal bacteria in ASD children generate more ammonia than their impaired liver can clear. This might happen if an oral antibiotic given for an ear infection killed useful intestinal bacteria, allowing colonization by harmful bacteria. Another pathogenic scenario implicates glutamate in vaccines. Hoernlein noted that vaccines—especially measles, mumps, rubella (MMR) contain hydrolyzed gelatin, a source of glutamate to preserve the viruses: “[T]he MMR vaccine...contains 10% free glutamic acid.” [150] She quoted Benarroch: “There is a low-affinity glutamate transporter that acts as a 1:1 cystine-glutamate exchanger and carries cystine to the interior of the cell in exchange for intracellular glutamate...Accumulation of extra-cellular glutamate inhibits the cystine-glutamate exchanger, resulting in depletion of cell stores of cystine” [151]. Cystine is a major precursor of sulfur amino acids.

Ammonia releases glutamate from neurons, and glutamic acid (amino acid substrate of glutamate) can release ammonia [46]. Ammonia may also be high in children weaned before six months old because solid food has much more protein than breast milk. Axelson: “When other foods are introduced during the weaning period the protein intake increases remarkably to 3–4 g/kg/day in spite of the fact that the protein requirement is decreasing, ...[T]he metabolic effects with high levels of urea in serum and urine, and the high levels of many amino acids may exceed the capacity of the hepatic and renal systems to metabolize and excrete the excess of nitrogen.” [152] Infant formula often has more protein as well.

### Table 1

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1. Fever often relieves autistic behavior, often dramatically, and rarely aggravates [40–43,62].

2. ASD children often have high blood ammonia [2,3] and loss of executive functions [34,61].

3. Ammonia in the brain induces a “frontal lobe syndrome” with loss of executive functions [13]; accumulation of ammonia shifts brain metabolism and blood flow from cortex to subcortex [12].

4. Children with high brain ammonia and glutamine from urea cycle disorders rarely show autistic behavior [1,16]. Partial deficiencies of urea cycle enzymes do show autistic behavior [14]—do they accumulate more ammonia than glutamine? If high brain glutamine protects children from ASD but not from brain swelling, how can that help? Yet researchers remain unconvinced that glutamine causes the astrocyte swelling of ammonia [14,60].

If astrocyte glutamine synthetase normally functions near maximum capacity [12], can UCD children have much more brain glu-
tamine than ASD children? They can if glutamate transport into astrocytes is impaired in ASD as Wakefield suspected [4]. But why do impaired executive functions in ASD correlate with low glutamate/glutamine in the subcortex of the brain not the cortex [34]?

Might fever relieve autistic behavior simply via extracellular sodium displacing brain calcium? Ammonia shifts calcium into astrocytes [153]; evidence of calcium accumulation in ASD brains has been detected [79]. Yet fasting increased brain calcium in rats [154]. Stress-induced adrenal cortical steroids move calcium into brain neurons [155]; does prednisone do the same? Furthermore, high brain ammonia (thus high brain calcium?) in UCD rarely shows autistic behavior. One explanation may be evidence that glutamine reduced Ca2+ accumulation in cultured neurons [156].

Another critical question: why are boys 4x more vulnerable to ASD than girls? Larger muscles in boys synthesize and accumulate more glutamine, but boys eat more protein, generating more ammonia. Esbjörnsson et al. studied plasma ammonia after sprint exercise in healthy males and females: "In conclusion, the lower plasma ammonia after sprint exercise in females seems to be explained by a lower accumulation of ammonia in skeletal muscle and by a buffering of ammonia in the form of glutamine in females. The greater reduction in plasma leucine in males seems to be related to their greater increase in muscle ammonia after sprint exercise." [157].

Norenberg et al. concluded that ammonia may cause astrocytes to swell via oxidative stress – effects of reactive oxygen species like free radicals and peroxides [158]. Rossignol and Frye found that physiologic/metabolic studies of autism in recent years focused largely on four concerns: oxidative stress, immune dysregulation/inflammation, mitochondrial dysfunction, and environmental toxins [159]. The intracellular peptide glutathione protects against oxidative stress by scavenging free radicals, detoxifies heavy metals (notably mercury), and is required for liver enzymes that detoxify organic toxins like drugs [160]. Most glutathione is formed in the liver from amino acids cysteine, glutamate, and glycine; glutamine readily serves as glutamate for this reaction [85]. Shabert also noted that glutamine is the primary fuel source for lymphocytes and macrophages of the immune system, and a required nutrient for antibodies that line the intestinal, respiratory, and genitourinary tracts [85]. Thus glutamine may protect against oxidative stress, immune dysregulation, and impaired liver detoxication in ASD.

A preliminary version of this paper was sent to several hundred ASD practitioners formerly listed on the ARI site, for feedback. Fourteen replies suggest ASD practitioners commonly give oral glutamine to heal the intestines, from 250 mg to 8 g/day, with few side effects (some hyperactivity) but few notable improvements in behavior – but see Williams [57].

Practitioners and researchers describe autistic behavior as “heterogeneous” (varied, dissimilar) because each child's behavior looks relatively unique. Yet autistic behavior is also very distinctive, rapid, and stereotyped. The behavior released looks different in each child, but the release is similar.

One explanation may be that β-adrenergic stimulation by epinephrine moves taurine into cells, but intense β-stimulation reverses this shift. Durlach and Durlach: “[β]Intense β-stimulation produces reverse effects on cell [taurine] influx: instead of an increase, a decrease is observed.” [105] Because calcium moves with taurine under β-stimulation [106], does intense β-stimulation ‘flush’ calcium from the brain?

A thought experiment: Suppose fever relieves autistic behavior by some means other than release of muscle glutamine. If so, then any child who improves from fever is not harmed by the increase in blood glutamine (nor the ammonia/glutamate it generates) even if he isn't helped. This might mean glutamine/ammonia/glutamate makes things worse but fever more than compensates their aggravation. Possible – but plausible? Another possibility is that fever helps only those children without high blood ammonia, who can detoxify ammonia from muscle glutamate. But children with high blood ammonia presumably get fevers as often as other children – yet fever rarely aggravates autistic behavior, even when it doesn't relieve. res ipsa loquitur

Tests and remedies

Blood tests cannot distinguish fever responses from stress responses to the test in children terrified of blood drawing. Blood ammonia is best detected via glutamine or orotic acid concentrations in urine [12,162]. Distinguishing brain glutamine from glutamate by MRS usually requires an ultra-high (7 Tesla) field [163], but a method at 3T has been reported [164]. Muscle glutamine concentrations by MRS may also be revealing; children who do not improve from fever may have muscles most depleted of glutamine (and protein). When blood glutamine is low, muscle glutamine is probably very low [85]. The most revealing MRS measurements may be brain metabolites critical to energy metabolism and ammonia detoxication (notably glutamine, glutamate, creatine, phosphocreatine, taurine, and GABA) in children who improve most dramatically from fever, especially when improvements persist days after fever ends. This should distinguish brain metabolites that rise and fall with temperature from metabolites that rise and fall with behavior.

Low-protein diets are usually recommended when blood ammonia is high, but Stevens et al. reported that protein deficiency in rats preserved ammonia to form amino acids, whereas a high-protein diet improved tolerance to ammonia: “[W]e suggest that malnourished children may be more than normally vulnerable to the hyperammonemic syndrome.” [165] Córdoba et al. concluded a normal-protein diet was safe for patients with hepatic encephalopathy [166], as others have. One wonders if glutamine-free diets help ASD children because less protein means less ammonia – a risky strategy – yet these diets do help [43,167].

Good food sources of glutamine include cabbage, beets, beef, chicken, fish, beans, and dairy products [168]. Woelker recommends 500 mg–1000 mg oral glutamine daily (between meals) for ASD children, to improve gut health, muscle tone, and overall metabolism [55]. Exercise stimulates muscles to take up ammonia and synthesize glutamine [19], but also increases ammonia [157]. Although supplemental glutamine can elevate blood/brain ammonia when the liver is impaired, body-builders and athletes ingest large amounts of glutamine daily; great amounts have been safely given in severe catabolic states [85,169,170]. Branched-chain amino acids detoxify ammonia [18] and synthesize glutamine [169]. Although tumors consume glutamine avidly, glutamine supplements do not stimulate their growth [19]. Mg and B6 are cofactors for conversion of glutamate to glutamine. Depletion of thiamine (vitamin B1), a cofactor for α-ketoglutarate dehydrogenase, has been implicated in ASD [171]. Arginine is the primary mitochondrion that rise and fall with temperature from metabolites that rise and fall with behavior.
detoxifier of blood ammonia, and substrate for creatine and nitric oxide. Arginine's precursor citrulline is better utilized by the body; watermelon is a good source of both [172]. High arginine vasopressin in ASD [173] may further deplete arginine, constrict brain vessels directly [174], and induce hyponatremia. Salt cravings from stress-induced hyponatremia may best be sated with oral rehydration salts [146,175]. Another remedy may be inulin (source of fructose) and oligosaccharides (short sugar polymers) to replace harmful intestinal bacteria with useful bacteria; lactobacillus strains may be added [176].

Creatine is highest in animal protein, especially pork and tuna, also beef, chicken, fish, and soybeans. Used freely by athletes to energize muscles, 1–2 g/day improved alertness and cognition in dementia and Alzheimer's [94]. Woeller recommends 500 mg creatine monohydrate 2/day to begin for ASD children 3–6 years old, then 1000 mg (1 g) 2/day, then an average maintenance dose of 1.5–3 g/day; he has given these children 5–10 g/day without adverse effects [101]. Creatine must be buffered with plenty of fluids to flush the kidneys and protect the liver. Personal experience indicates oral creatine monohydrate energizes the brain remarkably, to calm the emotional mind.

Conflict of interest statement

None.

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