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# Intergenerational Metabolic Syndrome and Neuronal Network Hyperexcitability in Autism

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## Abstract

We review evidence that suggests a role for excessive consumption of energy-dense foods, particularly fructose, and consequent obesity and insulin resistance (metabolic syndrome) in the recent increase in prevalence of autism spectrum disorders (ASD). Maternal insulin resistance, obesity and diabetes may predispose offspring to ASD by mechanisms involving chronic activation of anabolic cellular pathways and a lack of metabolic switching to ketosis resulting in a deficit in GABAergic signaling and neuronal network hyperexcitability. Metabolic reprogramming by epigenetic DNA and chromatin modifications may contribute to alterations in gene expression that result in ASD. These mechanistic insights suggest that interventions that improve metabolic health such as intermittent fasting and exercise may ameliorate developmental neuronal network abnormalities and consequent behavioral manifestations in ASD.

### Keywords

acetylome; autism spectrum disorder; diabetes; GABA; high fructose corn syrup; ketone bodies; mTOR; obesity; sociality

## Metabolic Syndrome Adversely Affects Brain Development

Considering the recent increase in obesity and diabetes rates and the concomitant rise in Autism Spectrum Disorder (ASD) diagnoses, the present review compiles evidence for the possible causal relationship between metabolic syndrome and ASD, and thus the potential beneficial contribution of metabolic interventions. Metabolic syndrome is a pathophysiological state that is characterized by insulin resistance, obesity, systemic inflammation and disengagement of adaptive cellular stress response pathways. Metabolic syndrome often results from excessive energy intake and a sedentary lifestyle, and predisposes individuals to chronic disease states including obesity, type 2 diabetes,

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cardiovascular disease, stroke and dementia [1, 2]. In this context, we address three major questions: 1) What are the cellular and molecular mechanisms by which metabolic syndrome alters brain development in ways that result in the behavioral manifestations of ASD? 2) Does gestational metabolic syndrome increase the risk for ASD by epigenetic reprogramming of gene expression in the developing fetal brain? 3) Can interventions that improve metabolic health of conceiving parents reduce the risk for ASD in their children, and will such interventions also benefit children already diagnosed with ASD?

There has been a dramatic increase in obesity rates in the United States over the past 50 years (Figure 1). A major cause of this recent epidemic of metabolic syndrome is the increased consumption of simple sugars, and particularly high-fructose corn syrup in soft drinks and many processed foods [3, 4]. Indeed, high-fructose diets can cause insulin resistance and obesity and can impair cognition [5–7]. While adult obesity is a major health crisis, even more disconcerting is features of metabolic syndrome in children and conceiving parents [8]. Studies of humans and animals have established that insulin resistance and obesity adversely affect synaptic plasticity and cognition by mechanisms involving oxidative stress, neuroinflammation and compromised neurotrophic and neuroprotective signaling [1,2, 9, 10]. Human and animal studies show that maternal obesity and diabetes predispose offspring to poor metabolic health and associated diseases [11, 12]. Conversely, neuroplasticity (synaptogenesis and neurogenesis), cognition and neuroresilience are enhanced by intermittent dietary energy restriction/fasting and exercise, both of which improve metabolic health [1, 13]. The developing prenatal and early postnatal brain is especially vulnerable to altered metabolic states, with major implications for the cognitive and behavioral outcomes of children born to metabolically unhealthy parents. Moreover, children born to parents who consume excessive amounts of simple sugars are likely to adopt such diets even as they become independent adults [14].

In the present article we describe how the recent increases in the prevalence of insulin resistance and obesity may be causally associated with the increase in ASD prevalence. Accumulating evidence supports a major role for excessive dietary energy intake and consequent metabolic abnormalities during fetal and early postnatal development in the pathogenesis of ASD. Children with ASD exhibit accelerated brain growth during infancy which is associated with increased synaptogenesis and hyperexcitability of neuronal networks involved in sociality, affective behaviors, cognition and language [15]. Because neuronal network hyperexcitability is a pervasive feature of ASD [16, 17], we focus on the mechanistic links between metabolic syndrome and the development and function of glutamatergic and GABAergic circuitry. To this end, we draw upon associational data from studies of human populations, advances in the genetic causes of ASD and risk for it, as well as studies of animal models of ASD. A better understanding of how metabolic states affect brain development and the etiology of ASD can enlighten parents and physicians as to how they can act to increase the likelihood of positive cognitive and emotional health outcomes of developing children.

## Coalescence of the ASD and Metabolic Syndrome 'Epidemics'

In the 1980s autism prevalence in the United States was reported as 1 in 10,000, but by 2013 that rate had increased to almost 1 in 50 according to the Centers for Disease Control [18]. This 200-fold increase (Figure 1) is due in part to increased awareness of the disorder and its symptoms among parents and educators. Rates have also increased due to a broader definition of Autism Disorder in the 5$^{th}$ edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V) in 2013. The DSM-V combined three disorders that were defined separately in the DSM-IV (Asperger's Disorder, Autism Disorder and Pervasive Developmental Disorders Not Otherwise Specified) under one umbrella disorder: Autism Spectrum Disorders. Behavioral features of ASD include social withdrawal and repetitive behaviors, often accompanied by deficits in cognition and language development (DSM-5). Children with ASD often avoid making eye contact with others and may insist on restricted and invariant daily activities. The replacement of the word "autism" with the term "ASD" recognizes the fact that there is a wide range of symptom severity and functional impairment among children with ASD.

Increased awareness and recognition of ASD behavioral symptoms in children does not fully account for the recent increase in ASD prevalence. There is also a major contribution of exposure to environmental factors during gestation and early childhood to ASD [20]. Toxicants reported to increase ASD risk due to prenatal and/or postnatal exposure include heavy metals such as mercury and lead, air pollutants, pesticides and polychlorinated biphenyls [21]. However, the establishment of direct causation of ASD by toxicant exposure requires further experimentation in animal models. Postnatal exposure to vaccines was falsely implicated as a driver of ASD symptoms and despite this claim having been discredited many times the idea that vaccines cause ASD regrettably still persists today [22]. Other aspects of the prenatal environment that can affect ASD risk include maternal infection, nutrition, and obesity [23].

With regards to the prevalence of metabolic syndrome, in the 1960s and 1970s, around 10% of American adults were considered obese; by the 2010s that number increased to over 30% (Figure 1) [24, 25]. There is a vast literature investigating the cause of the obesity epidemic. The preponderance of evidence points to two major contributors to the rise in obesity: increasingly sedentary lifestyles, and increased availability and consumption of inexpensive foods high in glucose, fructose and/or saturated fats [26, 27]. A high-fructose diet affects metabolism by stimulating the production of triacylglycerols and branched chain amino acids (leucine, isoleucine and valine), which increase adiposity [5, 28]. Studies in rodents have shown that a high-fructose diet during pregnancy results in insulin resistance and obesity in offspring [29, 30]. Additionally, the pups of female rats which consume fructose while nursing show neuroendocrine and metabolic abnormalities [31].

Trends in obesity and ASD prevalence as well as correlational studies in humans and experiments in animals point towards a possible causal relationship between maternal metabolic syndrome features and ASD. Consistent with a role for excessive energy intake in ASD, the increase of ASD prevalence in the U.S. tracks with the increase in daily calorie intake (Figure 1b). Recent findings bolster the case for a cause-effect relationship between

increased fructose consumption and ASD (Figure 2). Consumption of high-fructose corn syrup results in impaired hippocampus-dependent learning in adolescent rats, which is associated with neuroinflammation [32]. Cognitive deficits resulting from high fructose consumption may be mediated by the effect of fructose on brain derived neurotrophic factor (BDNF). When female rats are provided with fructose, but not glucose, in their drinking water during gestation, their offspring exhibit BDNF gene promoter hypermethylation and reduced hippocampal BDNF expression, which is associated with impaired hippocampus-dependent cognition [33]. In humans, young adults with a genetic mutation causing BDNF haploinsufficiency score higher than controls on an ASD behavioral rating scale indicating more ASD-like symptoms [34]. Fructose may also have direct effects on neuronal signaling pathways that result in impaired regulation of behavior and energy metabolism. For example, fructose administration impairs the ability of glucagon-like peptide 1 to suppress appetite [35]. This may explain why fructose stimulates food intake. Brain imaging studies suggest that compared to glucose, fructose affects neuronal network activity in brain regions involved in functions often impaired in ASD, such as executive control in the prefrontal cortex [36–38].

## Genetics Implicate Perturbed Metabolism and Neuronal Network Excitability in ASD

Estimates of the heritability of ASD range from 10 – 50% depending upon the type of study and the cohort examined [39]. An unusual feature of ASD genetics is that most of the dominantly inherited mutations thus far discovered are genetic variants found in the affected child but not in either of their healthy parents. These *de novo* variants (single-base pair mutations or single- nucleotide variants) presumably arose in the germline (egg or sperm) of one of the parents [40]. We speculate that environmental factors that result in unhealthy cellular energy metabolism contribute to the de novo mutations that increase ASD risk. Genes linked to ASD encode proteins known to play roles in a number of key physiological functions including: (i) energy and protein metabolism (e.g., phosphatase and tensin homolog, branched chain ketoacid dehydrogenase kinase, ubiquitin-protein ligase E3A, fragile X mental retardation protein and tuberous sclerosis 1); (ii) neuronal gene expression (e.g., methyl CpG binding protein, chromodomain helicase DNA-binding protein 8, RNA binding protein, fox-1 homolog, and dual specificity tyrosine phosphorylation regulated kinase 1A); (iii) axon and dendrite outgrowth (reelin, focal adhesion kinase, slit homolog 2 and testican 1); and (iv) synaptic plasticity (e.g., SH3 and multiple ankyrin repeat domains 3, voltage-gated sodium channel alpha subunit 2A, NMDA receptor subunit 2B, fragile X mental retardation protein, neurofibromin 1, aminomethyltransferase and calcium voltage-gated channel subunit alpha 1C) [39, 40]. Mutations in some of these genes are inherited in a dominant manner (e.g., *FMR1, CHD8, DYRK1A* and *GRIN2B*) while others are inherited in a recessive manner (e.g., *BCKDK* and *AMT*). Gene expression (mRNA) analyses of brain tissue samples from ASD patients compared to controls provide evidence of aberrant gene expression in pathways involved in metabolism and the regulation of neuronal network activity [41]. In addition, pro-inflammatory genes are upregulated in ASD, consistent with the well-known association of inflammation with metabolic syndrome [42].

Proper brain functioning requires a balance between the activity of excitatory glutamatergic neurons and inhibitory GABAergic neurons (Figure 3). An imbalance between these two systems may contribute to ASD. Many mutations that increase the risk for ASD are found in genes involved in glutamatergic and GABAergic neurotransmission. These include genes encoding the NMDA receptor subunit 2B, a subunit of voltage-dependent $Na^+$ channels (voltage-gated sodium channel alpha subunit 1A) and several proteins comprising postsynaptic membrane-associated complexes involved in structural and functional synaptic plasticity (SH3 and multiple ankyrin repeat domains 3, synaptic Ras GTPase-activating protein 1, and reelin). A recent review article described the links between epilepsy and ASD, and the involvement of neuronal network hyperexcitability in ASD pathogenesis [17]. A role for reduced GABAergic inhibitory tone in ASD is suggested by reduced levels of transcripts that are highly enriched in fast-spiking GABAergic neurons (Box 1). These transcripts encode the $Ca^{2+}$-binding protein parvalbumin and a $Ca^{2+}$ sensor for transmitter exocytosis [43]. The clustering of ASD-associated genes in pathways involved in metabolism or neuronal network excitability is consistent with the hypothesis that metabolic syndrome is responsible, at least in part, for the excitatory imbalance in ASD [44].

## Animal Models Support the Metabolic Syndrome – Hyperexcitability Hypothesis of ASD

Mouse models of ASD exhibit altered molecular and cellular mechanisms that converge on metabolism and neuronal network excitability. These models have been reviewed recently from a behavioral perspective, and exhibit social withdrawal, anxiety, repetitive behaviors and/or cognitive inflexibility [45, 46]. Here we focus on mouse models of ASD that provide evidence of hyperexcitability in the pathology of ASD. These include models of fragile X and Rett syndromes as well as Tsc2 and SH3 and multiple ankyrin repeat domains 3 (SHANK3) knockout mice. Fragile X syndrome (FXS) is the most common form of inherited ASD and is caused by CGG repeat expansions in the *FMR1* gene on the X chromosome [47]. These expansions result in polyarginine repeats in the fragile X mental retardation protein (FMRP) and the ASD-like behaviors that are seen in FXS. An early study of FMRP knockout mice demonstrated reduced expression of the Kv4.2 $K^+$ channel protein in hippocampal neurons, which would be expected to increase excitability [48]. Supporting a role for reduced $K^+$ channel function in neuronal hyperexcitability in FXS, patch-clamp recordings from hippocampal pyramidal neurons in FMRP-deficient mice reveal a reduction of $Ca^{2+}$-activated $K^+$ currents and an associated decrease in the action potential threshold [49]. FMRP knockout mice also exhibit hyperactivation of the mechanistic target of rapamycin (mTOR) pathway [50], which is associated with aberrant accumulation of several dendritic proteins and impaired autophagy [51]. Stimulation of autophagy using RNA interference-mediated inhibition of the mTOR pathway reverses synaptic abnormalities and behavioral deficits in FXS mice [51] suggesting a novel approach for the treatment of ASD.

The mTOR pathway plays a role not only in FXS pathology, but also in other models of ASD and in metabolism. When levels of glucose and amino acids are relatively high, as occurs after eating a meal, mTOR is active and enhances phosphorylation of the S6 kinase. S6 kinase is a major positive regulator of overall protein synthesis that places cells in a

growth mode [1]. Thus, it might be expected that excessive dietary energy intake during pregnancy will promote rapid proliferation of neural stem cells and outgrowth of neurons during brain development. In addition to FXS, the mTOR pathway is dysregulated in mouse models of tuberous sclerosis complex (TSC). TSC is an ASD caused by variants in the genes encoding TSC1 or TSC2, two proteins that normally inhibit the mTOR pathway. The variants that cause TSC result in a hyperactive mTOR pathway [52]. Tsc2 heterozygous knockout mice exhibit hyperactive mTOR, impaired dendritic spine pruning, impaired autophagy and ASD-like behavioral abnormalities. Treatment with the mTOR inhibitor rapamycin prevents dendritic spine abnormalities in $Tsc2^{+/-}$ mice [53]. In sum, mTOR pathway activity is upregulated after eating and hyperactive mTOR signaling leads to abnormal neuronal morphology, and possible hyperexcitability of neurons in mouse models of ASD. However, the roles of mTOR signaling pathway abnormalities in neuronal network dysregulation in developmental brain disorders are complex. TSC2 and FMRP mutant mice, for instance, exhibit opposite changes in metabotropic glutamate receptor-mediated synaptic plasticity [54].

Another ASD marked by hyperexcitability of neuronal circuits is Rett Syndrome, which is caused by mutations in the *MECP2* gene [55]. Mice lacking methyl CpG binding protein (MECP2) in GABAergic forebrain neurons exhibit multiple autistic behaviors which apparently result from reduced production and release of GABA from those neurons [56]. Imaging of voltage-sensitive dyes in hippocampal slices revealed marked hyperexcitability of CA1 and CA3 pyramidal neurons in *Mecp2* mutant mice [57]. Interestingly, overexpression of MECP2 can also cause ASD – as occurs in MECP2 duplication syndrome – suggesting that MECP2 expression is normally tightly regulated [58]. Transgenic mice overexpressing MECP2 at about twice the normal levels exhibit dendritic overgrowth and abnormalities in layer 5 pyramidal neuron synapses. This overexpression of MECP2 also leads to greater dendritic spine density compared to controls during the early postnatal period, but then spine density in these mutant mice falls below normal after 3 months of age [58]. The latter study provided evidence that S6 kinase (a target of mTOR) is hyperphosphorylated in somatosensory cortex of MECP2 transgenic mice, consistent with a role for hyperactivation of the mTOR pathway in developmental abnormalities. Because hyperactivation of the mTOR pathway in brain cells and ASD-like synaptic and behavioral abnormalities occur in animals fed diets high in sucrose or saturated fat [10, 59–61], the findings that genetic manipulations that increase mTOR pathway activity result in ASD-like behavioral abnormalities support the metabolic syndrome hypothesis of ASD.

Several ASD mouse models directly impact proteins that regulate neuronal excitability and cell growth. Mice lacking SHANK3 exhibit ASD-like social behaviors and hyperexcitability of cortico-striatal-thalamic circuits [62]. Selective deletion of SHANK3 from striatal inhibitory neurons results in repetitive exploratory behaviors, whereas deletion in only forebrain excitatory neurons results in abnormal self-grooming [63]. *Shank3* haploinsufficiency results in more subtle cognitive deficits and impaired long-term potentiation at hippocampal CA1 synapses [64]. Animal models of idiopathic ASD (BTBR mice) and monogenic ASD (*Shank3*, *Gad65* and *Mecp2* knockout mice), also display impaired multisensory integration, likely originating from insular cortex abnormalities [65]. In ASD patients, functional imaging studies have revealed abnormal neuronal network

activity in the insular cortex, which integrates sensory information and is functionally connected to brain regions that mediate attention and cognition [66]. Thus, studies in SHANK3 deletion models of ASD provide further evidence that mutations in genes that increase ASD risk also increase neuronal excitability.

In addition to the genetic mutations mentioned thus far, animal studies indicate that diet-induced obesity can predispose to neuronal hyperexcitability and ASD-like symptoms. The possibility that metabolic syndrome can increase the risk of ASD is supported by studies showing that a high-energy diet exacerbates behavioral abnormalities in mice genetically predisposed to ASD-like behaviors [67]. Moreover, offspring born to dams on a high-energy diet exhibit ASD-like abnormalities in social and repetitive behaviors [68]. The mechanism may involve adverse effects of the high-energy diet on the gut microbiome because the social deficits in the pups can be reversed by reconstituting their gut microbiome with flora from animals fed a normal diet or with a specific strain of bacteria (*L. reuteri*) [69]. Interestingly, when dams that had been fed a high-energy diet during gestation were switched to a normal diet during lactation, the adverse effect of the in utero metabolic environment on the offspring's behavior was ameliorated [70]. Altogether, studies of animal models establish compelling associations between abnormalities in energy and protein metabolism, neuronal network excitability, and ASD-like behaviors.

## Imaging Brain Alterations in ASD

Contributing to an understanding of metabolic abnormalities and associated structural and functional alterations of the brain in ASD have been magnetic resonance imaging (MRI) studies of children and young adults diagnosed with ASD in comparison with age-matched neurologically normal controls. There have also been efforts to establish ASD biomarkers based on quantitative analyses of images acquired by MRI and to correlate features of these images with behaviors. Numerous studies have reported structural alterations in gray matter associated with ASD [71]. Using voxel-based morphometry and a multivariate pattern analysis approach, Uddin et al. found that children and adolescents with ASD exhibit differences from controls in the default mode network (DMN) including the medial prefrontal cortex, posterior cingulate cortex and parahippocampal gyrus), as well as the posterior parietal cortex and lateral temporal lobe [72]. Their data also revealed significantly greater volumes of PCC and supramarginal gyrus, and they found that the structural abnormalities in the PCC were associated with poorer communication scores in the Autism Diagnostic Interview-Revised tests. However, a more recent larger study of nearly 600 research participants (ages 6–35 years) enrolled in the Autism Brain Imaging Data Exchange achieved less than 60% classification accuracy in discriminating ASD cases from controls [73]. The latter study used linear and non-linear discriminant analysis to classify based gray matter volume, cortical thickness and cortical surface area. Therefore, structural MRI analyses to date have not yielded clear correlations between ASD symptoms and altered brain structure.

In contrast to structural MRI-based biomarkers, analyses of functional MRI (fMRI) data appear more promising for biomarker development. Findings from fMRI studies reveal correlations between alterations in brain regional connectivity and behavioral manifestations

of ASD. In particular, multiple studies suggest associations between connectivity alterations and the degree of impaired sociality [74]. Several independent studies reported that compared to typically developing children those with ASD exhibit hyperconnectivity between the DMN and the executive control network, and that this abnormality is correlated with social deficits in ASD (Figure 1) [75–79]. Other fMRI studies suggest that there is abnormal functional connectivity of the hippocampus and the executive control network [80]. The main reasons for developing reliable biomarkers for ASD are for use in early or presymptomatic diagnosis, for monitoring disease progression, and for evaluation of the effectiveness of interventions in clinical trials. However, because the brain alterations underlying ASD are believed to occur in early development and behavioral abnormalities can be detected in children as young as 3 years of age, early diagnosis based on brain imaging would require acquiring images in utero or in infants.

## Maternal Metabolic Syndrome and ASD

Studies on the effects of maternal metabolic syndrome on offspring show strong associations with ASD risk. A meta-analysis of thirteen studies concluded that maternal obesity and overweight are significantly associated with increased ASD diagnosis in offspring [81], as well as ASD-like traits in offspring not diagnosed with ASD [82]. Gestational weight gain (the amount of weight gained by the mother from conception to birth of the child) is also associated with ASD in offspring [83]. Women who fall above or below the recommended amount of gestational weight gain are at a higher risk of having a child with ASD [83]. Related to obesity, pre-gestational diabetes (diabetes diagnosed in the mother before pregnancy) and gestational diabetes also contribute to ASD prevalence in offspring. A case-control study of children 2–5 years old with or without ASD demonstrated a significantly higher incidence of metabolic syndrome in mothers of children with ASD compared to those with neurologically normal children. Children with or without ASD born to mothers with features of metabolic syndrome scored lower on tests of expressive language and adaptive behavior compared to children born to healthy mothers [84].

One mechanism by which maternal metabolic syndrome may influence ASD risk is by altering synaptic plasticity in offspring. Synaptic plasticity can be evaluated in children by continuous theta burst stimulation (cTBS) using transcranial magnetic stimulation (TMS). Normally, a single TMS pulse results in a motor evoked potential (MEP), whereas the repetitive stimulation during cTBS causes a progressive reduction of MEP amplitudes. Children whose mothers had gestational diabetes do not show a suppression of MEP amplitudes in response to cTBS, and greater maternal insulin resistance was correlated with reduced MEP amplitude suppression in those children [85]. These findings indicate that children of metabolically unhealthy mothers display reduced neuronal adaptability to changing stimuli.

Although both diabetes and obesity are considered metabolically unhealthy states, they may act via distinct mechanisms regarding their impact on ASD etiology. For example, one study suggested that maternal diabetes delays embryonic development whereas diet-induced obesity accelerates development [86]. This increase in growth due to obesity may also be a driving factor of increased risk of ASD in the offspring of mothers with obesity. The brains

of newborns with ASD have been found to grow more quickly in the first year of life than healthy controls [87]. Additionally, one study found that the higher the rate of cortical growth, the greater the severity of ASD symptoms in infants [88]. Another study induced pluripotency in cultured cells derived from individuals with and without ASD and promoted their differentiation into neurons. The neurons derived from the cells of individuals with ASD grew more quickly and exhibited more complex branching those of the control group [89]. Taken together, these results indicate that it may be obesity itself, and not diabetes that drives the connection between metabolic syndrome and ASD. At the molecular level, the transgenerational transfer of metabolic syndrome risk as well as ASD prevalence may arise from epigenetic mechanisms (Box 2; Figure 4). In a woman with maternal metabolic syndrome, her developing fetus is exposed to many of the same adverse factors present in her blood including elevated levels of glucose, insulin and pro-inflammatory cytokines [90, 91]. It remains to be determined whether these circulating factors are responsible for her children having an increased risk for ASD.

## Metabolism-Based Interventions for ASD

Due to the high comorbidity of metabolic disorders, neuronal network hyperexcitability and ASD, interventions that improve metabolism and constrain neuronal excitability may reduce the number of children with ASD and improve the symptoms of those already diagnosed with ASD [92–94]. Interventions that appear promising include exercise, intermittent energy restriction/fasting, ketogenic diets, and dietary supplements/drugs that modify cellular metabolism and/or GABAergic neurotransmission (Table 1). We speculate that diet and exercise interventions that reverse metabolic syndrome will help women who are overweight and those with diabetes reduce the risk for ASD in their offspring. We further suggest that diet and exercise interventions, and drugs that enhance GABAergic tone may ameliorate behavioral deficits in children and adults with ASD.

Exercise has beneficial effects on behavioral symptoms in individuals with ASD [95]. Recent reviews document small to medium beneficial effects of exercise on ASD behaviors, but these benefits vary depending on the exercise protocol and the behaviors assessed [96, 97]. Exercise results in the greatest improvement in on-task duration (how long participants remained engaged on a task) and simple learning tasks [96]. Exercise interventions could be tailored to the needs of individuals with ASD, especially because children with ASD are less likely to be active due to motor and sensory impairments, reduced sociability (hinders engagement in team sports), and preferences for specific and predictable activities [93]. Indeed, a meta-analysis found that individuals with ASD benefit more from individual exercise interventions than from group interventions [98]. In overweight pregnant women, exercise has been shown to be a safe and effective way of improving metabolism and reducing abnormal acceleration of fetal growth [99]. Whether maternal exercise will reduce the risk of ASD in offspring remains to be determined. Exercise can protect neuronal circuits against hyperexcitability [100] which might contribute to beneficial effects in ASD. BDNF and fibroblast growth factor 2 (FGF2) are exercise-induced neurotrophic factors that play key roles in the regulation of synaptic plasticity and control of neuronal hyperexcitability [101, 102]. Levels of FGF2 are lower in children with ASD and levels are negatively

correlated with ASD severity [103]. Moreover, children and young adults with a genetic reduction in BDNF expression exhibit more ASD-like behaviors compared to controls [34].

Based upon the evidence that intermittent fasting enhances GABAergic tone, and improves cognition and lessens anxiety [104], we speculate that intermittent fasting may provide another non-pharmacological intervention for improving ASD symptoms. Fasting leads to a 'metabolic switch', in which cells switch from using glucose as their primary fuel source to using ketones. Alternating the metabolic challenges of fasting and exercise with resting and eating results in "intermittent metabolic switching" (IMS). The benefits of IMS on brain health include increased mitochondrial biogenesis in neurons, increased activity of neurotrophic factors, and reduced oxidative stress and inflammation [1]. Of greatest relevance to the treatment of maternal metabolic syndrome and ASD, IMS increases levels of ketone bodies, resulting in upregulated GABAergic tone, increases in BDNF levels and inhibition of the mTOR pathway. In practice, intermittent fasting improved behavioral deficits in a phosphatase and tensin homolog (PTEN) deficiency mouse model of ASD [105] but has yet to be tested in women with maternal obesity or children with ASD. Ketogenic diets (KD) mimic the metabolic switch to ketones, without the need for fasting, by eliminating sources of glucose from the diet and increasing sources of ketones. KDs ameliorate neuronal network hyperexcitability and behavioral deficits in ASD mouse models [106, 107], and there have been several reports of beneficial effects of KDs on behavioral symptoms in ASD patients in open-label design studies [108, 109]. 95, 96]. Apart from ketogenic diets, recent studies have shown that dietary provision of a ketone ester (β-hydroxybutyrate) can reduce anxiety and improve cognition in mice by a mechanism involving suppression of hippocampal neuronal network hyperexcitability [110].

Studies of animal models and humans have shown that obese individuals have an altered gut microbiota, and that fecal transplantation of gut bacterial flora can improve glucose metabolism and reduce obesity [reviewed in ref. 111]. Children born to mothers with an unhealthy gut microbiota are at increased risk for ASD, and children with ASD often exhibit gut dysbiosis [reviewed in ref. 112]. A fecal transplant study in mice showed that obese-type gut microbiota during pregnancy results in ASD-like behaviors in offspring that are more pronounced in males [113]. Recent preliminary findings suggest that fecal microbiota transplants can improve behavioral symptoms in children with ASD [114].

While GABA receptor agonists seem a logical pharmacological approach for mitigating neuronal network hyperexcitability in ASD, clinical trials in children and adolescents with ASD have produced mixed results [115]. Other pharmacological approaches that target the same metabolic pathways as exercise and intermittent fasting have been reported to be effective in ASD animal models. One such approach is to bolster cellular $NAD^+$ levels with nicotinamide riboside to support GABAergic interneurons [116, 117]. mTOR is another attractive target for pharmacological intervention in ASD as both fasting and exercise decrease mTOR activity [1]. An increase of mTOR pathway activity in ASD correlates with reduced dendritic spine pruning and reduced autophagy [53]. Treatment of BTBR mice with the mTOR inhibitor rapamycin ameliorates ASD-like behaviors [118]. Drugs that improve glucose metabolism, such as metformin and GLP-1 receptor agonists, also merit investigation for potential applications to the treatment of maternal obesity and ASD patients

(Table 1). As obesity rates continue to rise throughout industrialized countries, lifestyle and/or pharmacological interventions may be necessary to combat the concomitant increase in the prevalence of ASD.

## Concluding Remarks and Future Directions

Genetic and epidemiological studies of ASD patients and their relatives, as well as the development of animal models, have enabled a better understanding of the molecular and cellular alterations underlying the behavioral manifestations of ASD. Accelerated growth of neural progenitors and of neurons during brain development results in aberrant connectivity and hyperexcitability of cortical microcircuits in ASD. Such hyperexcitability is caused in part by a deficit of PV-expressing fast-spiking GABAergic interneurons. This excitatory imbalance increases seizure susceptibility, but also appears to account for many of the behavioral abnormalities of ASD. In the present article we have reviewed evidence suggesting a major role for metabolic syndrome in the rapid increase of ASD prevalence that has occurred in the U.S. during the past 40 years. Children born to mothers who are obese and/or diabetic are at increased risk for ASD. Sedentary lifestyles and the consumption of high amounts of high fructose corn syrup are believed to contribute to many instances of obesity and diabetes.

The adverse consequences of metabolic syndrome on brain development, cognition and mood are now well established [1, 119, 120], but are not yet widely appreciated. The emerging evidence for a cause – effect relationship between metabolic syndrome and ASD underscores the need to better educate parents on the effects of obesity on the mental health of their children. Medical communities, relevant branches of government and private foundations have a responsibility to disseminate the implications of research on metabolic syndrome and ASD to the public. Family physicians and pediatricians should routinely council prospective parents of the potential detrimental effects of maternal, and possibly paternal, overweight, obesity and diabetes on the mental health of the children they conceive. Efforts to reduce childhood obesity via education of parents, teachers, physicians, and children themselves should be a priority.

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## Glossary

**Acetylome**
The entire set of protein acetylations of a cell or organism

**Epigenetic modifications**
molecular modifications of DNA, histones and other chromatin-associated proteins that can result in changes in gene expression; examples include methylation, acetylation and ubiquitination

**Intelligence**

the ability to acquire or infer, and retain information, and then apply it towards adaptive behaviors within an environment or occupation

**Intermittent fasting (IF)**
a feeding pattern that includes periods of time of sufficient length to deplete liver glycogen stores and elevate blood ketone levels

**Ketogenesis**
the process by which the ketone bodies β-hydroxybutyrate and acetoacetate are produced from fatty acids in hepatocytes during periods of food deprivation/fasting

**Metabolic syndrome**
a pathophysiological state that is characterized by insulin resistance and obesity, and aberrant cell growth and disengagement of adaptive cellular stress response pathways including autophagy

**mTOR**
mechanistic target of rapamycin is a serine/threonin protein kinase that is core component of two different protein complexes that positively regulate protein synthesis and cell growth and negatively regulate autophagy

**Neuroresilience**
the ability of the nervous system to adapt to stressful environmental conditions so as to maintain and restore and enhance the structure and function of neuronal networks

**Prefrontal cortex**
the most anterior region of the frontal cortex which plays a major role in decision making; it uses information about the current behavioral context to rapidly generate goals based on the current biological needs

**Sociality**
the extent to which an individual interacts with other individuals and integrates into social groups

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**Box 1.**

## GABAergic dysregulation in ASD

GABAergic neurons play a critical role in reining in neural activity, and may be dysregulated in ASD, resulting in increased neuronal activity and excitability [121]. By inhibiting neighboring glutamatergic pyramidal neurons, GABAergic interneurons constrain excitatory signaling and thereby control action potential generation and timing (Figure 3). There are three major types of GABAergic interneurons in the cerebral cortex that are distinguished by their expression of specific proteins, their electrophysiological properties, and where they form synapses on pyramidal neurons [122–124 109–111]. The most prevalent type of interneuron, and the type that data suggest is dysfunctional in ASD, expresses the $Ca^{2+}$-binding protein parvalbumin (PV), has a very high spiking frequency, and innervates the soma and proximal dendrites of pyramidal neurons [125]. The other two types of interneurons express either somatostatin or the serotonin receptor 5HT3a and have lower spiking rates [122]. A prominent source of excitatory input to cortical PV interneurons is from neurons in the thalamus which transmit visual, auditory and tactile sensory inputs. Electrical stimulation of thalamic neurons results in excitation of cortical pyramidal neurons and, after a short delay, hyperpolarization mediated by activation of adjacent PV interneurons. In addition to controlling the firing rate of pyramidal neurons, PV interneurons contribute to gamma frequency oscillations (25–89 Hz), which facilitate cognitive processing [123]. Gamma oscillations are reduced in ASD patients which may result from GABAergic neuron dysfunction [126].

Studies of human subjects and animal models suggest a major role for PV interneuron dysfunction in the prefrontal cortex in ASD. Measurements of GABA levels using magnetic resonance spectroscopy demonstrated an association of tactile hypersensitivity with reduced GABA levels in the sensorimotor cortex of patients with ASD compared to controls [127, 128 114, 115]. Levels of glutamic acid decarboxylase and PV are reduced in cortical interneurons in ASD [129, 130 116, 117], suggesting reduced production of GABA in those neurons. DNA methylation is altered in ASD compared to controls at sites associated with multiple genes, several of which are involved in GABAergic neurotransmission [131]. Moreover, when mice are reared in social isolation, they exhibit ASD-like behaviors which are associated with reduced PV expression and reduced numbers of PV interneurons in brain regions affected in ASD [132]. Aberrant signaling via the metabotropic glutamate receptor mGluR5 is implicated in Fragile X syndrome and other ASDs. Targeted disruption of mGluR5 in PV interneurons in mice results in decreased inhibitory postsynaptic currents in pyramidal neurons, impaired brain oscillatory activity, compulsive behaviors and impaired sociality [133].

Reduced function or loss of GABAergic interneurons in ASD suggests a therapeutic potential for interventions that activate GABA receptors on glutamatergic neurons or that preserve and/or restore functional GABAergic neurons. In two different 16p11.2 mouse models of ASD, long-term treatment with the $GABA_B$ receptor agonist baclofen improved cognitive performance and social interactions [134]. Although there is mixed evidence for altered $GABA_A$ receptor availability in ASD [135], treatment with the $GABA_A$ receptor agonist diazepam during an early period of postnatal development

(P15–28) rescues multisensory integration deficits in the BTBR T+tf/J mouse model of ASD [64]. There was no improvement in multisensory integration when the drug was administered later at P45–58 [65]. The latter finding has important implications for the treatment of children with ASD, as it suggests that early diagnosis and intervention is critical. However, excessive activation of GABA receptors can impair cognition and social interaction [124] and therefore drugs that target GABA receptors generally have a narrow therapeutic window (see Figure I).

**Box 2.**

## Epigenetic metabolic reprogramming and dysregulated brain development

Epigenetic mechanisms are those that result in enduring changes in gene expression that occur without changes to the base sequence of the DNA itself. Epigenetic mechanisms include, but are not limited to DNA methylation, histone post-translational modifications, changes in nucleosome positioning, histone variants, microRNAs and long non-coding RNAs [136 123]. The role of epigenetic mechanisms in mediating the effects of maternal metabolic states on offspring have been most intensively studied in the context of transference of obesity risk [137]. In the brain, global and gene-specific DNA hypomethylation has been documented in the offspring of obese female mice in comparison to non-obese females [138]. Hypomethylated genes include those involved in dopaminergic and opioid signaling which are known to regulate nutrient sensing and food intake. A high-fat diet during pregnancy resulted in site-specific histone modifications in developing fetuses in monkeys [139]. These histone modifications were associated with altered expression of genes known to regulate food intake, circadian rhythms and energy metabolism in a manner expected to promote obesity in the offspring. The offspring of dams with diet-induced obesity had liver cells exhibiting dysregulation of circadian core clock genes and genes involved in energy metabolism including PPARα and SIRT1 [140]. Altered PPARα expression was associated with altered histone modifications near the transcription start site of the gene [141].

The metabolic state of pregnant females can affect the epigenome of cells in their offspring. The epigenome is the complement of molecular modifications of DNA and histone that affect gene expression and can be passed on to offspring via epigenetic inheritance. Peripheral tissues of offspring of obese mice and non-human primates, whose metabolic syndrome was induced by high carbohydrate and high fat diets, exhibit altered histone acetylation [140, 142]. Another mechanism by which poor diets, and thus unhealthy metabolic states, may result in epigenetic changes in brain cells is via the gut microbiome [143]. Bacterial composition of the microbiome is reconfigured fairly quickly after dietary intervention [144, 145, 131]. Alterations to the microbiome result in variations in microbial metabolites, such as short chain fatty acids and urolithins, which can directly alter levels of histone modification [146–148]. The mechanisms by which the gut microbiome affects epigenetic modifications of gene expression in brain cells remain to be determined.

Beyond metabolic syndrome, several types of epigenetic modifications have been linked to ASD as well (Figure 4). Epigenetic mechanisms altered in ASD include DNA methylation, folatemethionine pathway enzymes, and histone acetylation [149]. Of the 16 genes marked as having “high coincidence” with ASD in the Simons Foundation Autism Research Initiative (www.sfari.org), about half are directly or indirectly linked to epigenetic changes [150]. Proteins encoded by these genes include those that play a role in chromatin structure (ARID1B, SETD5, SUV420H1, and TBR1) or in transcription (ADNP, ASH1L, ASKL3, chromodomain helicase DNA-binding protein 8, POGZ) [150]. Other genetic mutations that increase the risk of ASD and intellectual disability are found in *Dnmt3A* (encodes a DNA methyltransferase) [151] and *Huwe1* (encodes a protein that

ubiquitinates histones) [151]. Genetic disorders with high incidences of ASD that are also caused by mutations in genes that alter epigenetic mechanisms include Rett and Sotos syndromes. Rett syndrome results from a mutation in the *Mecp2* gene, which results in the misreading of epigenetic markers [152]. Sotos syndrome is a product of mutations in *Nsd1*, which encodes histone H3K36 methyltransferase and the mutated form modifies histones. Epigenetic markers of ASD include altered DNA methylation [Summarized in 153] and histone acetylation [154, 155]. However, the location and direction of these epigenetic alterations vary depending on the study due to differences in ASD cohort composition, sample tissue type, and methodology used [153].

## Outstanding Questions

What are the molecular mechanisms that result in altered formation of neuronal circuits as a consequence of metabolic syndrome in utero and during early childhood development?

Will future epidemiological and experimental studies establish whether or not high fructose intake during pregnancy is a major cause of the recent increase in the prevalence of ASD?

Can lifestyles that incorporate exercise, intermittent energy restriction, and avoidance of simple sugars and of processed foods prevent ASD?

Can physiological and pharmacological interventions that enhance GABAergic ‘tone’ mitigate behavioral symptoms in children and adults with ASD?

## Highlights

The rapid increase in the prevalence of autism spectrum disorders (ASD) during the past 40 years is associated with excessive dietary energy intake, particularly fructose, and a concomitant increase in metabolic syndrome (obesity, insulin resistance and hyperlipidemia).

Children born to mothers with metabolic syndrome and/or diabetes are at increased risk for ASD.

Studies of humans and animal models suggest that ASD involves accelerated growth of neural progenitor cells and neurons resulting in aberrant development of neuronal circuits characterized by a relative GABAergic insufficiency and consequent neuronal network hyperexcitability.

Genes associated with ASD encode proteins involved in protein synthesis, cell growth and synaptic plasticity, and epigenetic molecular modifications implicated in ASD pathogenesis impact the expression of genes in the same pathways.

Intermittent fasting, exercise, and avoidance of fructose prevent metabolic syndrome, normalize neuronal network excitability and ameliorate ASD-like behaviors in animal models.

Interventions that prevent and reverse metabolic syndrome in conceiving parents and their offspring may prove beneficial in reducing ASD prevalence and symptom severity.

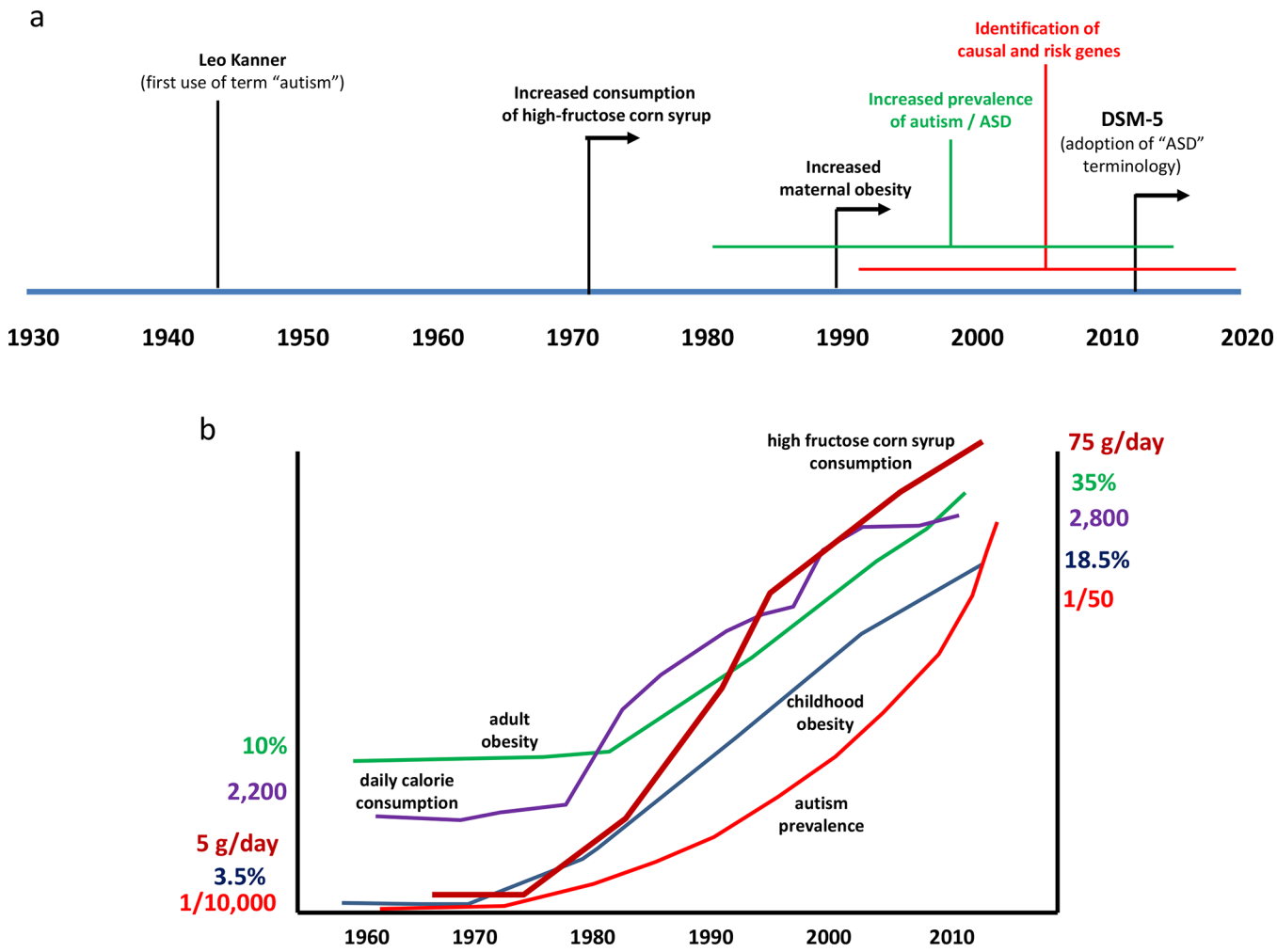


**Figure 1.**

Temporal association of the increase of metabolic syndrome and ASD prevalence in the U.S. **a.** Historical timeline. Before Asperger's published description of children exhibiting social isolation [161], Leo Kanner at Johns Hopkins University provided the first description of 11 autistic cases [162] and thereafter systematically studied autistic children [163]. In 2013 the revised version of the DSM-5 adopted the term ASD. **b.** High-fructose corn syrup was widely incorporated into soft drinks and processed foods beginning in the early 1970s which contributed to a rapid increase in per capita calorie intake and adult and childhood obesity. The increases in maternal obesity and autism prevalence lagged behind the increases in fructose consumption and obesity by about 20 years consistent with a role for maternal metabolic syndrome in ASD pathogenesis. The values on the y axes of the graph indicate the lowest value (left) and highest value (right) for each plot on the graph and are color-coded to correspond with the lines on the graph. This graph was prepared using data available from the U. S. Centers for Disease Control and Prevention (https://www.cdc.gov/DataStatistics/).

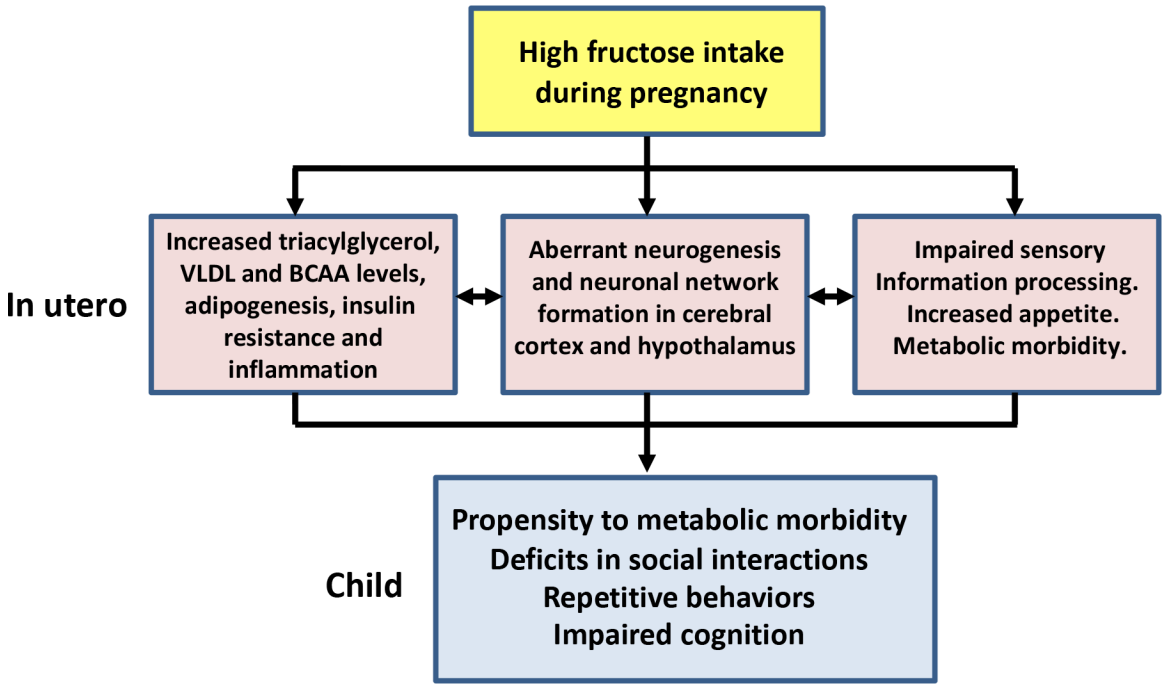


**Figure 2.**

Maternal metabolic syndrome model for the pathogenesis of ASD. Parental diets high in fructose accompanied by sedentary lifestyles combine with genetic and epigenetic factors to predispose children to ASD. The metabolic state of the pregnant female influences brain development in the developing embryo. Maternal obesity and insulin resistance may result in excessive activity of the mTOR pathway and impaired autophagy in neural stem cells and developing neurons, as well as a pro-inflammatory milieu. As a consequence, there is an acceleration of development of neuronal circuits which exhibit an abnormal increase in the ratio of excitatory glutamatergic synapses relative to inhibitory GABAergic synapses. Hyperexcitability of neuronal circuits in the cerebral cortex and hippocampus result in the behavioral abnormalities of ASD.

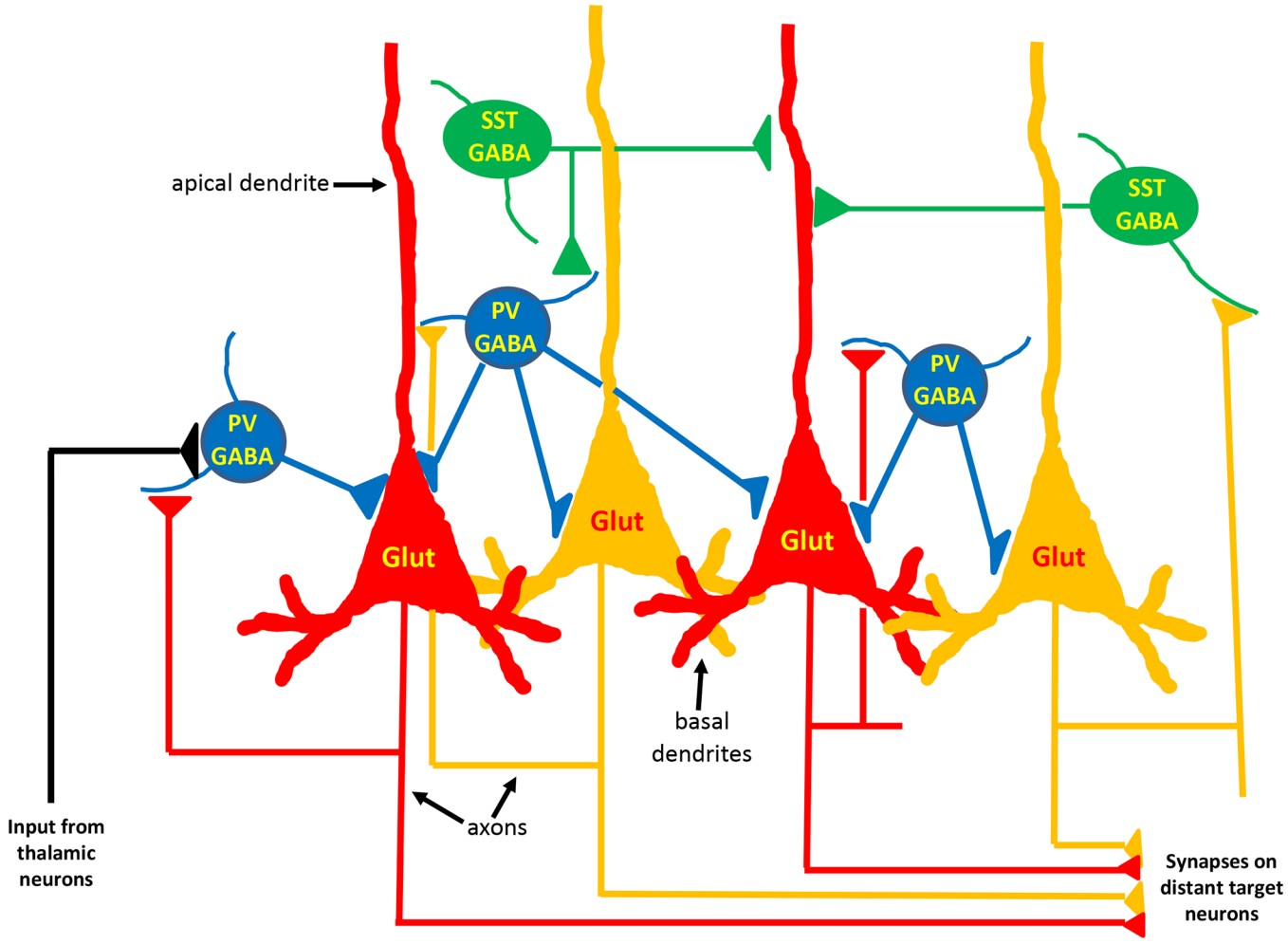


**Figure 3.**

Core neuronal circuits throughout the cerebral cortex are comprised of excitatory glutamatergic pyramidal neurons (Glut) and inhibitory GABAergic neurons. Glutamatergic pyramidal neurons have large elaborate apical and basal dendritic arbors and an axon that forms synapses on other glutamatergic neurons in the same or distant brain regions. Glutamatergic axons also synapse on adjacent GABAergic interneurons. Two types of GABAergic interneurons are illustrated, those that express parvalbumin (PV) and those that express somatostatin (SST). The PV interneurons synapse on cell bodies of pyramidal neurons, while SST interneurons synapse on distal regions of pyramidal neuron dendrites. Each interneuron forms synapses on several different pyramidal neurons.

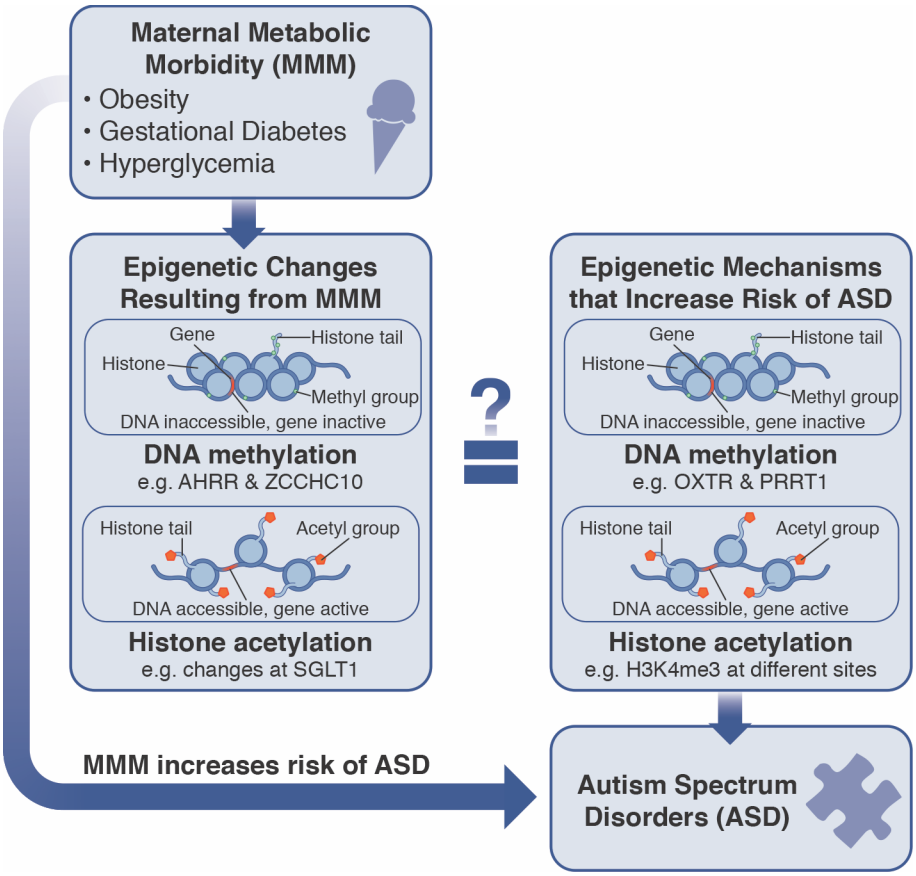


**Figure 4.**

Epigenetic changes arise as a result of maternal metabolic morbidity (MMM) and several epigenetic alterations that contribute to ASD risk. It remains to be determined whether there is an overlap between these two different clusters of epigenetic mechanisms. MMM results in altered DNA methylation (DNAm) and histone acetylation in the developing fetus and these changes persist into childhood. There are several studies showing that DNA methylation is altered in offspring of obese mothers. Examples of genes with altered DNAm in offspring as a result of maternal obesity include *Ahrr* and *Zcchc10* [164, 165]. Histone acetylation is also altered in the offspring of mice and primates that are fed a high fat/high carbohydrate (HF/HC) diet. For example, mice fed a HF/HC diet show increased acetylation of histone H3 at lysine 9 on the *Sglt1* gene, which induces *Sglt1* gene expression [141]. Altered DNAm and histone acetylation has also been implicated in the etiology of ASD. The outstanding question is whether the epigenetic changes in offspring that result from maternal metabolic syndrome are the same ones that lead to increased ASD risk. DNAm changes on genes such as *Oxtr* and *Prrt1* increase risk of ASD [166, 167], but studies of DNAm changes that predispose individuals to ASD are not often replicated and consensus is lacking.

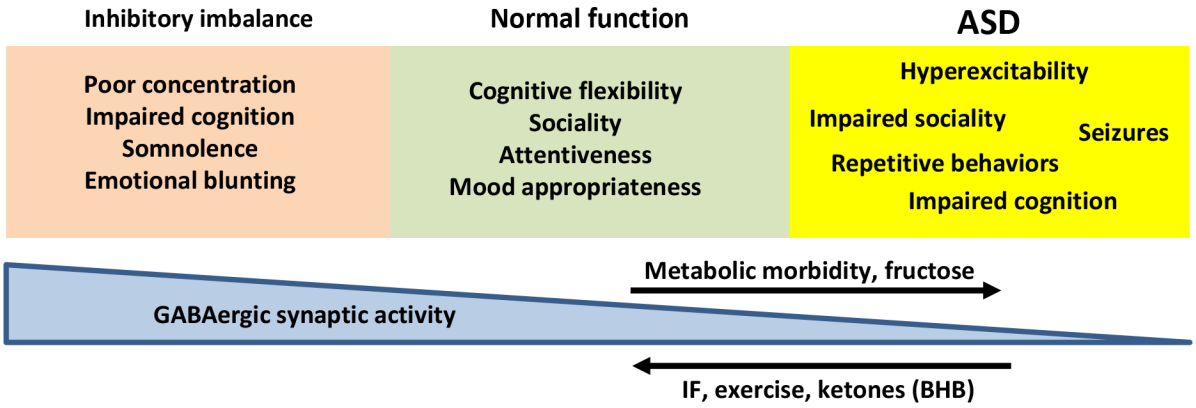


**Figure I, for Box 1.**

Maintenance of a controlled balance of excitatory and inhibitory neuronal network activities is required for normal brain function. Too much or too little GABAergic signaling results in abnormal brain function. An inhibitory imbalance can result in impaired cognition, sleepiness and reduced emotional responsivity. On the other hand, an excitatory imbalance can result in core features of ASD including impaired sociality and cognition and repetitive behaviors, as well as seizures. Metabolic syndrome may shift the excitation/inhibition (E/I) balance towards hyperexcitability. Intermittent fasting, exercise and the ketones can enhance GABAergic function and shift the E/I balance into the normal range. BHB, β-hydroxybutyrate.

**Table 1.**

Potential ASD interventions that act by improving energy metabolism and/or enhance GABAergic signaling.

| Intervention | Mechanism of Action (partial list) | Findings in ASD and animal models | References |
|---|---|---|---|
| **Intermittent fasting** | Enhances GABAergic tone; induces ketones and BDNF; inhibits mTOR | Enhances cognition in PTEN ASD mice | [104] |
| **Exercise** | Induces BDNF expression | Improves behaviors in ASD children and adults | [80, 84] |
| **Fecal transplant** | Improves energy metabolism | Lessens symptoms in children with ASD | [69, 100] |
| **Ketone (ester)** | Energy substrate; induces BDNF expression; Enhances GABAergic tone | Protects against pathological hyperexcitability; reduces anxiety, enhances cognition | [104, 156] |
| **Nicotinamide riboside** | Bolsters bioenergetics and sirtuin activity improves postpartum metabolic health in mothers | Improves cognition and motor function in mice pups | [104] |
| **Rapamycin** | mTOR inhibitor, autophagy inducer | Ameliorates ASD-like behaviors in mouse models | [157] |
| **Exendin-4, liraglutide** | GLP-1R agonist, insulin sensitizer induces BDNF expression | Improves multiple behaviors in ASD adolescents | [158] |
| **Metformin** | Inhibits liver glucose production, activates AMP, inhibits mTOR | Ameliorates behavioral deficits in fragile X mice | [159] |
| **GABA R agonists** | Activate GABA receptors | Constrains aberrant neuronal hyperexcitability | [160] |