

Narrative Review

Could Alzheimer's disease be a maladaptation of an evolutionary survival pathway mediated by intracerebral fructose and uric acid metabolism?

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ABSTRACT

An important aspect of survival is to assure enough food, water, and oxygen. Here, we describe a recently discovered response that favors survival in times of scarcity, and it is initiated by either ingestion or production of fructose. Unlike glucose, which is a source for immediate energy needs, fructose metabolism results in an orchestrated response to encourage food and water intake, reduce resting metabolism, stimulate fat and glycogen accumulation, and induce insulin resistance as a means to reduce metabolism and preserve glucose supply for the brain. How this survival mechanism affects brain metabolism, which in a resting human amounts to 20% of the overall energy demand, is only beginning to be understood. Here, we review and extend a previous hypothesis that this survival mechanism has a major role in the development of Alzheimer's disease and may account for many of the early features, including cerebral glucose hypometabolism, mitochondrial dysfunction, and neuroinflammation. We propose that the pathway can be engaged in multiple ways, including diets high in sugar, high glycemic carbohydrates, and salt. In summary, we propose that Alzheimer's disease may be the consequence of a maladaptation to an evolutionary-based survival pathway and what had served to enhance survival acutely becomes injurious when engaged for extensive periods. Although more studies are needed on the role of fructose metabolism and its metabolite, uric acid, in Alzheimer's disease, we suggest that both dietary and pharmacologic trials to reduce fructose exposure or block fructose metabolism should be performed to determine whether there is potential benefit in the prevention, management, or treatment of this disease.

Keywords: Alzheimer's disease, fructose, metabolic syndrome, insulin resistance, energy metabolism

Introduction

Alzheimer's disease (AD) is currently the sixth leading cause of death and is characterized by cognitive decline and cerebral atrophy associated with β -amyloid plaques and tau-protein aggregation (neurofibrillary tangles) in neurons. Treatments to reduce β -amyloid and/or tau protein aggregation carry promise but have generally not been as successful as predicted [1], consistent with a prior hypothesis [2] that more basic mechanisms may drive the disease. In this regard, preclinical and early manifestations of AD include reduced cerebral glucose metabolism, mitochondrial dysfunction, neuroinflammation, and intracellular energy depletion. These observations have led to

dietary, behavioral, and therapeutic strategies to improve metabolic parameters with promising early results [3–5]. Nevertheless, the underlying mechanism(s) driving AD, especially the late-onset sporadic variant, is not fully understood.

Here, we extend our previous proposal that AD results from a maladaptation to an evolutionary survival pathway that is used by many animals and was even essential to the survival of our distant ancestors millions of years ago [6]. A basic tenet of life is to ensure enough food, water, and oxygen for survival. Although acute survival responses to starvation [7] are well known, nature has developed a way to protect animals before the crisis actually occurs [8]. We have previously shown that this “survival response” is mediated by the metabolism of fructose

Abbreviations: AD, Alzheimer's disease; AMPD2, AMP deaminase-2; ApoE4, Apolipoprotein E4; CMR_{glc}, cerebral metabolic rate for glucose; CSF, cerebral spinal fluid; FDG-PET, [¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography; GLUT, glucose transporter; HFCS, high-fructose corn syrup; IR-A, insulin receptor A; Irs2, insulin receptor substrate-2; KHK, ketohexokinase; MCI, mild cognitive impairment; OXPHOS, oxidative phosphorylation; V1b, vasopressin 1b.

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that is either ingested or produced in the body [8]. Although biological effects of fructose metabolism and its byproduct, intracellular uric acid, appear critical for the survival of many animals in nature, including our ancestors, in modern society, it appears to be overengaged, increasing the risk for metabolic syndrome, obesity, diabetes, and other conditions [9].

A key question is how the survival response affects brain metabolism and function given that the brain has high energy requirements, accounting for 20% of the daily amount of ATP used by the body despite constituting only 2% of the body mass. Because much of the protection of the survival pathway is mediated by a reduction in systemic ATP production and usage [8], one might wonder whether the survival switch also involves reducing brain energy expenditure so long as critical brain function is supported. Here, we review evidence that suggests that the survival pathway was beneficial in reducing the risk of starvation but, in today's environment, may predispose us to not only obesity and diabetes but also AD.

A Survival Pathway Triggered by Fructose

Many foods are known to have physiological effects in addition to their caloric content. For example, sugary beverages are particularly associated with the development of obesity and diabetes [10], and this has been proposed to be due to their fructose content [11, 12]. Indeed, excessive fructose ingestion can induce all components of metabolic syndrome [13]. This has been shown to be mediated by the ability of fructose to raise intracellular uric acid levels (which can occur despite no change in serum uric acid) [14] and to stimulate the synthesis and release of vasopressin [11, 15–18] rather than from the caloric metabolism of fructose.

Subsequent research has found evidence that animals in nature use excessive intake and metabolism of fructose to activate a survival response that prepares them for periods when food, water, or oxygen may not be adequately available [8]. Specific features of the survival switch are shown in Table 1. In general, the mechanism involves going into a “low-power” mode in which both ATP production and usage are reduced. This is accomplished by reducing energy metabolism at rest [19] while allowing sufficient energy for critical activities, such as foraging. Both food and water intake are encouraged by stimulating hunger and arousal (likely via orexin), blocking satiety (by inducing leptin resistance) and stimulating foraging [20–22]. The demand for oxygen is reduced by slowing mitochondrial respiration, with a shift toward glycolysis [23, 24]. The storage of fat and glycogen in the liver is encouraged by stimulating their production and inhibiting fatty acid oxidation, lipolysis, and glycogenolysis [15, 25, 26]. Glucose metabolism in muscles is reduced by decreasing glucose uptake (via insulin resistance) and inhibiting insulin secretion from the pancreas; this reduces total energy expenditure while providing more glucose to the brain, where insulin is not fully required for uptake [27, 28]. Fructose also stimulates the production of vasopressin in the hypothalamus [18], which helps conserve water by reducing loss by driving urinary concentration. Vasopressin also directly contributes to metabolic syndrome, including the development of obesity, by engaging the vasopressin 1b (V1b) receptor [16]. Accumulation of fat by vasopressin is another mechanism by which vasopressin conserves water because fat is a source of “metabolic” water when it is metabolized [29].

The cellular mechanism by which fructose induces the survival program is unique. In essence, the 2 major simple sugars—glucose and fructose—have opposing biologic effects. Glucose is the primary fuel for immediate energy demands, whereas fructose provides for future energy demands (Figure 1) [8]. Essentially, fructose causes a shift in

TABLE 1

Features of the survival switch. The primary goal is to protect animals from shortage of water, food, and oxygen

Features	Mechanism	Consequence
Hunger	Stimulation of orexin Low hepatic ATP Leptin resistance	Increased energy intake
Thirst	An increase in serum osmolality	Increase water intake Increase serum vasopressin
Foraging	Inhibition of glucose metabolism in regions of the brain	Maximize the finding of food
Reduced resting energy metabolism	Suppression of mitochondrial ATP production with stimulation of glycolysis	Decreased resting energy metabolism
Fat storage	Stimulation of lipogenesis, inhibition of fatty acid oxidation, and inhibition of lipolysis	Fat accumulation in the adipose tissue, blood, and liver
Maintain energy delivery to the brain	Reduce glucose utilization by muscle, with deference for the brain	Insulin resistance
Support the circulation to assure nutrient delivery	Increase BP by vasoconstriction Increase salt absorption in the gut and salt reabsorption by the kidneys	Raise blood pressure Induce salt sensitivity
Heighten innate immune response	Stimulate low-grade systemic inflammation	Increase uric acid and inflammatory biomarkers
Aid excretion of wastes in the setting of poor nutrient intake	Impair renal autoregulation Activation of the renal angiotensin system	Elevation of glomerular hydrostatic pressure to assist filtration

BP, blood pressure.

cell metabolism such that the energy generated from the calories ingested is preferentially stored as fat and glycogen instead of being immediately used for ATP generation, a maneuver that preserves energy balance.

The biochemical mechanism driving the survival response is initiated by the rapid depletion of ATP from the initial phosphorylation of fructose by the enzyme fructokinase (also known as ketohexokinase [KHK]) (Figure 1). The ATP levels are not immediately replenished because fructose 1-phosphate pools because of a slower flux through aldolase B. The cell responds to lower ATP levels by lowering AMP levels to maintain the energy ratio. AMP degradation is mediated by AMP deaminase-2 (AMPD2), which produces ammonia and, eventually, uric acid [30]. Uric acid translocates NADPH oxidase (nicotinamide adenine dinucleotide phosphate oxidase) to the mitochondria, where it causes oxidative stress, reducing fatty acid oxidation (blocking enoyl CoA hydratase) while inhibiting aconitase in the citric acid cycle [15, 31]. Uric acid also inhibits AMP-activated protein kinase [25]. The net effect is switching to a low-power mode in which production and usage of ATP are slowed down while intracellular ATP levels remain low [32].

The decline in intracellular ATP level functions as an alarm, initiating processes that induce all features of metabolic syndrome [8]. The 3 primary drivers appear to be fructose, its byproduct uric acid, and vasopressin; the latter being a driver primarily because of its actions on

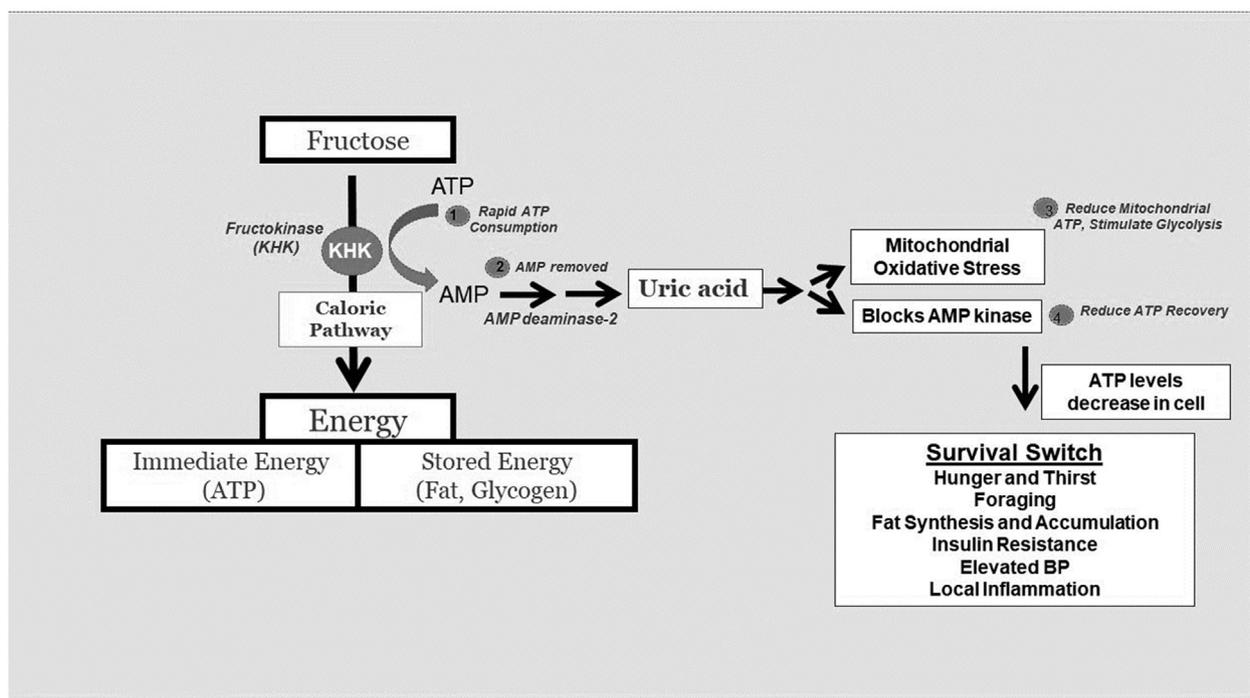


FIGURE 1. The fructose survival pathway. Fructose is metabolized by fructokinase to generate fructose-1-phosphate, which is then metabolized like any caloric sugar. However, the initial phosphorylation is associated with rapid ATP consumption with a decrease in intracellular phosphate that uniquely activates AMP deaminase-2, which subsequently removes AMP to generate uric acid. In turn, uric acid translocates NADPH oxidase (nicotinamide adenine dinucleotide phosphate oxidase) to the mitochondria, leading to oxidative stress that blocks the citric acid cycle (via inhibition of aconitase) and fatty acid β -oxidation. As mitochondrial function slows, glycolysis takes over, while uric acid inhibits AMP-activated protein kinase, reducing the ability to recover ATP. The effect is a reduction in ATP in the cell, activating a survival switch that includes hunger, thirst, foraging, fat accumulation, and insulin resistance. Shaded numbered circles show steps that assist in lowering ATP levels in the cell. BP, blood pressure; KHK, ketohexokinase.

the V1b receptor. Ultimately, the activation of the survival switch prepares the animal for a period of scarcity, resulting in increased body weight, enhanced fat and glycogen stores, insulin resistance, elevated blood pressure, salt sensitivity, and low-grade systemic inflammation (Table 1). This aids survival by increasing the energy stores required for hibernation, long-distance migration, nesting, or other situations in which food, water, and oxygen are less available.

In nature, dietary fructose from excessive intake of fruit provides a major pathway to activate this survival response, much like what occurs in the autumn when bears prepare for hibernation. However, fructose is also produced in the body via the polyol pathway, in which glucose is converted to fructose [32–36] (Figure 2). The rate-limiting enzyme in the polyol pathway is aldose reductase, and its activity is stimulated during times of stress, such as when nutrient delivery is impaired (hypoxia or ischemia) [32, 37], when water supplies are low (dehydration, hyperglycemia, and hyperosmolarity) [8], or when uric acid levels are high (reflecting degradation of nucleotides and ATP, suggestive of an energy crisis) [38].

Most fructose is metabolized in the liver and intestine, although some is metabolized in other tissues, such as the kidney and brain. However, it is the metabolism of fructose in the liver that is critical for inducing features of metabolic syndrome because mice that have fructokinase knocked out in the liver are protected from fructose-induced weight gain and metabolic syndrome [17]. Although intake of fructose is a major pathway to activate the biological switch, other foods can also stimulate fructose production in the body and induce features of metabolic syndrome (Figure 2) [14, 39, 40]. These include foods that provide the glucose substrate for the polyol pathway, such as high glycemic carbohydrates, and foods that stimulate aldose

reductase, such as salty foods and alcohol. Umami foods (especially processed red meats, organ meats, shellfish, and beer that is rich in yeast extracts) also engage the purine degradation pathway leading to uric acid [14, 39, 40] (Figure 2). These foods increase fructose production in the liver and other organs [36, 41], thereby activating the survival switch and inducing metabolic syndrome [14, 39, 40]. Indeed, the 3 tastes (sweet, salt, and umami) that identify pleasurable foods likely developed to stimulate the intake of foods that could activate the survival switch, whereas bitter and sour tastes help identify foods that might contain toxins [42].

Humans have put this biological switch into overdrive by the means of 2 historic events. First, we are more sensitive to the effects of fructose because the enzyme uricase was lost in our primate ancestors because of a series of mutations in the uricase gene millions of years ago, leading to higher uric acid levels [9] and a greater metabolic response to fructose [43, 44]. Indeed, this mutation likely provided a significant survival advantage that saved our species from extinction during the seasonal starvation that occurred in the middle Miocene subepoch [9].

The second more proximate factor has been the dramatic rise in the intake of added sugars that contain fructose and glucose, such as table sugar (sucrose) and high-fructose corn syrup (HFCS) [13]. The Western diet contains a high amount of fructose (primarily from sucrose and HFCS) and foods that stimulate fructose production (high glycemic carbohydrates, alcohol, and salty foods) or those that readily generate uric acid (umami-rich foods), all of which engage the survival switch. Thus, many humans are activating this survival mechanism intermittently, and the degree of activation is influenced by the amount and speed of ingestion [45] and genetic and environmental factors.

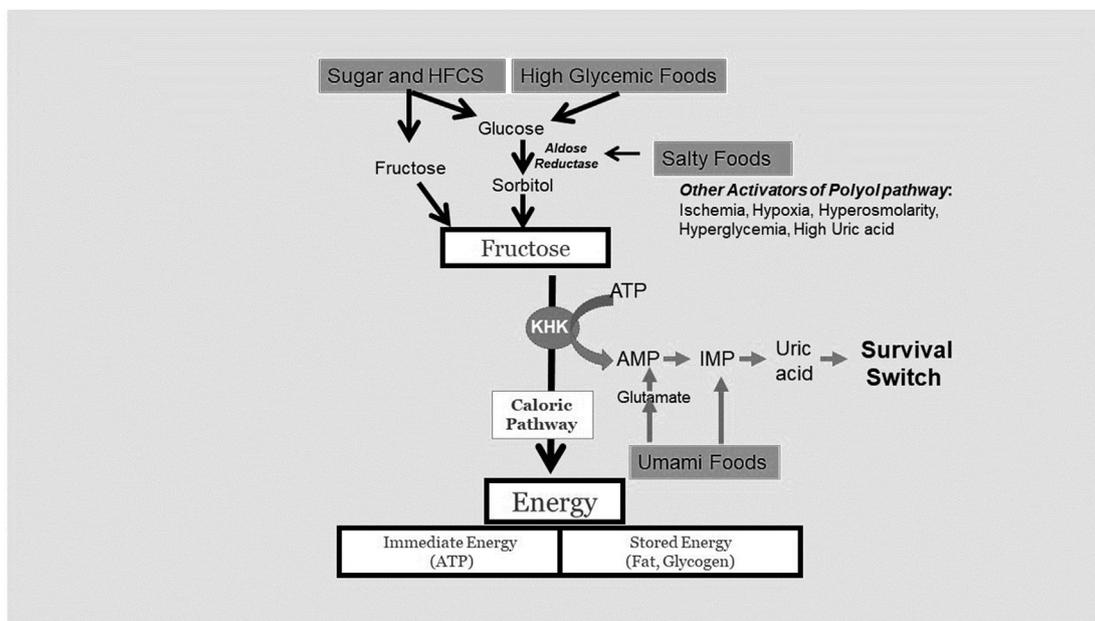


FIGURE 2. The process by which foods and stress engage the fructose survival pathway. Fructose can come directly from the diet (such as added sugars containing sucrose or high-fructose corn syrup [HFCS]) or from high glycemic carbohydrates. The latter provides excess glucose that can be converted via the polyol pathway to fructose because of activation of the rate-limiting enzyme aldose reductase. Aldose reductase can also be activated by high osmolality, which can result from ingestion of salty foods, high glycemic foods, or alcohol. In turn, the metabolism of fructose activates the survival switch. Interestingly, umami foods rich in glutamate and/or purines (such as AMP or inosine monophosphate [IMP]) can also activate the switch distal to the fructose step. KHK, ketohexokinase.

Interestingly, whole fruits tend not to activate this pathway owing to a relatively low fructose content in individual fruits and the presence of neutralizing factors (such as fiber, vitamin C, potassium, and flavanols) and because the small intestine metabolizes some fructose before it reaches the liver and brain [46].

Neuron Survival in the Resting and Hypoxic State

The human brain requires ~20% of the overall energy at rest, of which most is used by the neurons (70%–80%) [47]. The high energy needs of neurons are accomplished by mitochondrial oxidative phosphorylation (OXPHOS) of glucose, which requires sufficient oxygen to be present. The neurons themselves have a poor backup capacity because they generate very little ATP from glycolysis because of an impaired ability to upregulate phosphofructokinase [48]. β -Oxidation of fatty acids is also limited, which may relate to the higher oxygen requirements compared with glucose oxidation, enhancing the risk of local hypoxia [49].

The favored fuel for neurons is glucose, and experimental evidence has shown that providing glucose can improve cognitive responses to challenging tasks [50]. When blood glucose levels are low, the neighboring astrocytes provide fuel to the neurons. Astrocytes minimize their own energy and oxygen needs by relying on glycolysis. They then provide the lactate they generate to the neurons, which is used as a substrate for mitochondrial respiration (the lactate shuttle) [51]. Astrocytes also store glycogen that can be broken down to glucose during fasting, providing glucose to the neurons when systemic delivery is impaired [52]. In addition, the breakdown of fat during fasting releases ketone bodies from the liver that can be used by neurons to generate acetyl-CoA, which can assist mitochondrial

respiration; however, this fallback strategy provides only 60% of the energy needed by the brain [53].

The astrocyte has a key role in neuronal health in the setting of food or oxygen deprivation. Indeed, mild hypoxia upregulates glycolysis in cultured astrocytes while decreasing mitochondrial respiration [54]. This is linked with activation of the transcription factor HIF1- α with stimulation of fructose metabolism and insulin resistance pathways [54]. However, if stress is further increased, both glycolysis and OXPHOS are inhibited, which can lead to the death of the astrocyte. Experimental studies suggest that astrocytes can survive when incubated with A β amyloid by increasing glycolytic activity; however, if glycolysis is blocked, astrocytes develop reactive gliosis and die by apoptosis while A β amyloid accumulates further [55].

Fructose, Foraging and AD

The fructose survival pathway helps preserve critical brain functioning during starvation by inducing systemic insulin resistance that preferentially provides glucose to the brain (Table 2). The pathway also stimulates foraging, which costs energy; however, this is compensated for by reducing resting energy metabolism. However, given the brain's significant energy needs, how does this pathway affect cerebral energy metabolism?

Foraging involves a specific behavioral response. It requires rapid assessment (limiting deliberation), impulsivity (limiting self-control and reasoning), exploratory behavior, and risk-taking (limiting recent memory). Some aspects of foraging are mediated by stimulation of the anterior cingulate cortex and visual (occipital) cortex [56, 57]. The anterior cingulate is also involved in the hunger response to fasting [58]. However, much of the foraging response is enhanced by

TABLE 2
Beneficial effects of the fructose survival switch on brain function

Response	Mechanism	Outcome
Stimulate hunger	Stimulate orexin	Increase food intake and fat stores
Impair satiety	Induce central (hypothalamic) leptin resistance	Disrupt normal weight regulation
Induce metabolic syndrome	Vasopressin synthesis and release with engagement of V1b receptors	Stimulate fat production (metabolic water) and features of metabolic syndrome
Stimulate foraging	Reduce glucose metabolism in special regions of the brain	Enhance the ability to find food
Preserve Glucose Delivery to Brain	Induce Systemic Insulin Resistance Outcome	Reducing glucose uptake by muscle saves glucose for metabolism by the brain
Reduce energy metabolism in the brain	Reduce glucose metabolism in special regions of the brain	Help conserve overall energy needs

V1b, vasopressin 1b.

TABLE 3
Parallels between early Alzheimer's disease and intracerebral effects of fructose metabolism

Characteristic	Early Alzheimer's disease	Fructose metabolism
Factors associated with increased risk	Diet (sugar, high glycemic, and high salt) Phenotype (diabetes, obesity, and metabolic syndrome)	Diet (sugar, high glycemic, and high salt) Phenotype (diabetes, obesity, and metabolic syndrome)
Factors associated with decreased risk	Diet (vegetables and dairy)	Diet (vegetables and dairy)
Preferential regions affected	Hippocampus, entorhinal cortex, posterior cingulate cortex, middle temporal gyrus, and sensorimotor cortex	Hippocampus, posterior cingulate cortex, thalamus and cerebral cortex
Glucose metabolism	Decreased cellular uptake (decreased insulin receptors) Decreased metabolism	Decreased cellular uptake (decreased insulin receptors) Decreased metabolism
Bioenergetics	Decreased glycolysis (possible early stimulation) Reduced mitochondrial function Reduced ATP level	Decreased glycolysis (possible early stimulation) Reduced mitochondrial function Reduced ATP level
Fructose metabolic pathways	Increased AMPD2, increased fructose and sorbitol levels, and uric acid elevated in early disease	Increased sorbitol and fructose levels, increased AMPD2 activity, and increased uric acid in early disease

AMPD2, AMP deaminase-2.

inhibiting activity in the cortical regions involved in control and reasoning, by inhibition of the posterior cingulate cortex involved in disengagement from foraging [59] [60], and by inhibiting activity of the entorhinal cortex that reduces attention to time. Inhibition of recent memory (hippocampus and entorhinal cortex) also lessens the resistance to enter areas known to be dangerous, as does inhibition of the prefrontal cortex involved in self-control. Thus, the stimulation of foraging is coupled with significant regional reduction in brain energy metabolism, which could also conserve energy in low food availability settings (Table 3).

Several studies have evaluated the contrasting effects of fructose and glucose on brain metabolism and the foraging response [61–63]. Comparing fructose and glucose responses is difficult because, as mentioned, glucose can be converted to fructose in the body and vice versa [39, 64]. Indeed, if glucose is administered to maintain serum glucose levels of 200 mg/dl, fructose levels increase in the brain after ~30 min and peak at 2 h [65]. However, the studies that evaluated the differences between fructose and glucose in cerebral metabolism using BOLD MRI were performed early (~15 min), thus making it more likely to reflect true differences between fructose and glucose. The striking finding from these studies was that fructose reduced blood flow to the posterior cingulate cortex, the hippocampus, the thalamus, and the occipital cortex [61]; however, blood flow increased to the area of the visual cortex associated with food reward [63]. Cortical blood flow also decreased [62]. Fructose administration also stimulated hunger and desire for food [63]. These responses are consistent with a stimulation of the foraging response. In contrast, glucose inhibited blood

flow to the hypothalamus, thalamus, insula, anterior cingulate, and striatum [61] while stimulating blood flow to the cortex [62]. These responses are expected to inhibit not only the foraging response but also responses involving appetite and reward.

One of the earliest findings in AD is a reduction in glucose metabolism and intracellular ATP levels in the hippocampus, entorhinal cortex, posterior cingulate cortex, and middle temporal gyrus. In contrast, a study of AD has shown that the anterior cingulate and occipital cortex are typically spared [66]. This corresponds very well to how fructose affects these regions and is in opposite to that observed with glucose (Table 3).

We hypothesized that the fructose-dependent reduction in cerebral metabolism in these regions was initially reversible and meant to be beneficial. However, the chronic and persistent decrease in cerebral metabolism driven by recurrent fructose metabolism leads to progressive brain atrophy and neuron loss with all of the features of AD.

Evidence for Intracerebral Fructose Metabolism as a Contributor to AD

The brain can generate and metabolize fructose

Our hypothesis suggests that local fructose generation and metabolism may be the critical factor for how fructose induces AD because under normal circumstances, only 1%–2% of ingested fructose reaches the brain [67]. Indeed, the brain is capable of producing fructose. As

mentioned earlier, simply raising blood glucose levels increases brain fructose levels in healthy humans [65]. Raising serum osmolality in mice by dehydration or salty food also stimulates fructose production in the brain (hypothalamus) [18]. Dietary fructose may also increase fructose production in the brain, possibly by raising uric acid levels in the brain. For example, acutely raising serum uric acid increases uric acid in both the hypothalamus [40] and the hippocampus [68, 69] in association with local inflammation. In turn, uric acid stimulates fructose production and metabolism [36, 70].

The brain also expresses both fructokinase and AMPD2 [71, 72]. Fructokinase (KHK) activity is high in the brain, and the injection of fructose into the hypothalamus of rats causes local ATP depletion and hunger [71, 73]. Interestingly, most KHK appears to be the isoform A [74]. Although this isoform does not typically induce ATP depletion in the liver, the relatively lower affinity of the aldolase isozymes present in the brain (aldolase A and aldolase C) toward fructose-1-phosphate [75] makes it likely that fructose-1-phosphate will accumulate in the brain, leading to local phosphate depletion with activation of AMP deaminase, uric acid generation, and the subsequent reduction in ATP.

Risk factors for AD are associated with fructose metabolism

The risk of AD is known to be increased by diets high in table sugar (sucrose) or HFCS [76–78], high glycemic carbohydrates [78, 79], salty foods [80, 81], and alcohol [82]. Likewise, processed meats rich in umami also increase the risk of dementia [83, 84]. All of these foods are associated with fructose production or direct engagement of the fructose survival pathway [14, 39, 40, 85] (Table 3).

Aging is also associated with AD. Because diets high in carbohydrates and salt characterize much of the diets of the general population, chronic endogenous fructose production could potentially explain this association. Consistent with this hypothesis, chronic intake of a diet containing 50% carbohydrates caused aging-associated kidney disease despite being low in sugar (<5%) but was nevertheless completely prevented in mice unable to metabolize fructose (KHK-knockout mice) [86]. This suggests that long-term intake of a Western diet, which typically contains 50% carbohydrates, might generate enough endogenous fructose to increase the risk of AD. Other risk factors for AD include obesity, metabolic syndrome, insulin resistance, and diabetes [87–94], all of which are linked to the intake of foods that either contain fructose or stimulate fructose production. Traumatic brain injury is another risk factor for AD and results in local ischemia that is expected

to increase local fructose production. In fact, hypoxia stimulates fructose metabolism in astrocytes [54]. Likewise, in ischemic contused spinal cords in rats, there is local activation of the polyol pathway that mediates neuronal inflammation and loss [95].

Fructose is elevated in the brain of patients with AD

There is also evidence that fructose production and metabolism are increased in the brains of patients with AD, especially early in the disease before marked neuron loss and atrophy. One study used mass spectrometry to measure components of the polyol pathway in post-mortem regions of the brains of 9 subjects with AD and 9 age-matched controls. Sorbitol and fructose levels (both components of the polyol pathway) were significantly elevated, averaging 3–5-fold higher in all regions of the brain studied, including the hippocampus, entorhinal cortex, middle temporal gyrus, cingulate cortex, sensory and motor cortex, and cerebellum (Figure 3) [96]. One control subject also had high levels of fructose and sorbitol but had no premortem evidence of dementia; however, the patient had preclinical AD, as noted by low brain weight and Braak stage II histopathologic changes [96].

Fructose metabolism consumes ATP [30]. This phenomenon is associated with AMP accumulation that is metabolized by AMPD2 to generate ammonia, hypoxanthine, and, eventually, uric acid (Figure 1). Interestingly, the brains of individuals with AD have increased expression and activity of AMPD2, with no change in AMP deaminase-3 [72]. Early AD is also associated with the release of ammonia; however, this eventually decreases as the disease progresses [97, 99]. Fructose metabolism also produces large amounts of lactate [98]. Perhaps not surprisingly, lactate levels are 4-fold higher in the brains of subjects with early AD compared to controls with no AD [99].

A metabolomic study of cerebral spinal fluid (CSF) found higher hypoxanthine and xanthine levels in subjects with mild cognitive impairment (MCI) than in controls, and xanthine concentration was also higher in subjects with AD [100]. Uric acid levels were also 25% higher in subjects with than in normal controls, and uric acid correlated with total tau protein when controls, MCI, and AD measurements were combined [100]. Another study confirmed a positive association of serum uric acid with impaired cognitive function (determined by testing with the mini-mental state examination) in subjects with MCI [101]. In contrast, subjects with AD appeared to have lower brain uric acid levels than controls [102].

The observation that brain (or CSF) uric acid levels are higher in MCI and decrease as the disease progresses may be explained by the

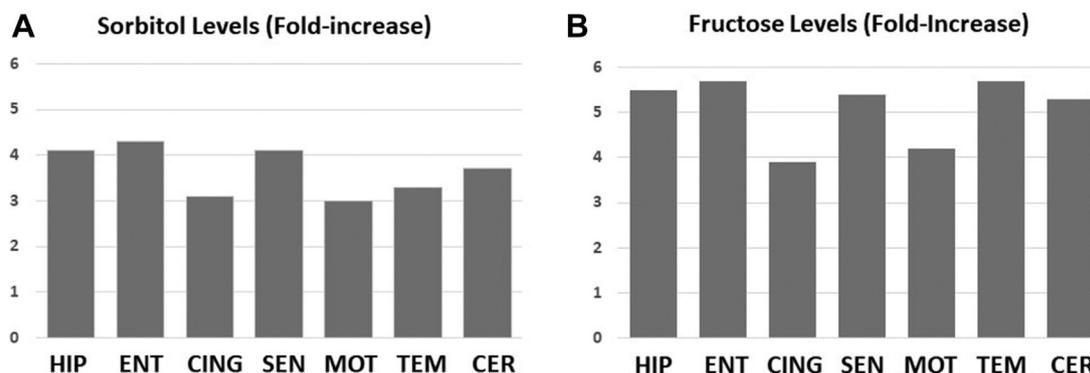


FIGURE 3. Evidence for activation of the polyol pathway in the brains of patients with Alzheimer's disease. The endogenous production of fructose can only occur from the conversion of glucose to sorbitol and then to fructose via the polyol pathway. One study found ~4–5-fold higher levels of both sorbitol (A) and fructose (B) in the postmortem brains of 9 patients with Alzheimer's disease compared with a similar number of controls [96]. CER, cerebellum; CING, cingulate gyrus; ENT, entorhinal cortex; HIP, hippocampus; MOT, motor cortex; SEN, sensory cortex; TEM, middle temporal gyrus.

progressive decrease in intracellular ATP production associated with progressive impairment in mitochondrial function. Because uric acid is largely generated from the degradation of ATP, less uric acid will be produced as ATP production and turnover decrease. Indeed, there is a decrease in brain ATP levels of ~7% in early AD that progressively worsens over time [103]. This might constitute a negative feedback system in an otherwise positive feedback system. We found that fructose induces less of a rise in uric acid in individuals with type 2 diabetes and obesity, which also could be explained by lower intracellular ATP production and turnover [104].

Could fructose metabolism contribute to cerebral glucose hypometabolism and mitochondrial dysfunction in AD?

Cerebral glucose hypometabolism and mitochondrial dysfunction in AD

An early finding in AD is a reduction in the cerebral metabolic rate for glucose (CMRglc), as measured by [¹⁸F]-fluoro-2-deoxy-D-glucose positron emission tomography (FDG-PET) scan [99, 105–107]. The primary sites involved are the hippocampus, entorhinal cortex, and parietal, temporal, and posterior cingulate cortex [105, 108]. This reduction in CMRglc is associated with a 50% reduction in ATP production from glucose metabolism and, overall, a 20% reduction in brain ATP production [109].

One mechanism for hypometabolism is decreased glucose uptake [108]. This is mediated in part by a reduction in glucose transporter (GLUT) 1 in the astrocytes and GLUT3 in the neurons of patients with AD [110, 111]. Although much of the brain does not require insulin for the uptake of glucose [112, 113], certain regions in the brain, such as the hippocampus, hypothalamus, striatum, and parietal and frontal regions of the cerebral cortex, are largely influenced by insulin [107, 114]. GLUT4 is the main glucose transporter that is insulin-dependent and is expressed in neurons in the hippocampus, hypothalamus, sensorimotor cortex, and cerebellum [110]. In AD, a reduction in both insulin and insulin receptor A (IR-A) is associated with insulin resistance [110, 115, 116]. Consequently, impairment in GLUT4 function occurs, which has a role in impairing cognitive function, especially in the hypothalamus [50].

Although decreased glucose uptake is one mechanism for reduced glucose metabolism, AD is also associated with a decrease in the activities of enzymes involved in glucose metabolism, including phosphofructokinase, phosphoglycerate mutase, aldolase, glucose-6-phosphate isomerase, and lactate dehydrogenase [110], which could reflect adjustment to a low ATP state. These findings are relevant because the resting state FDG-PET does not distinguish between a reduction in the availability of glucose or reduced use (demand). The possibility that the latter may be more important than commonly recognized is demonstrated by 2 studies that measured glucose levels in AD and found local glucose levels to be high [96, 111]. Furthermore, an FDG-PET scan performed with cognitive stimulation in subjects with early AD revealed increased CMRglc and blood flow [117]. This suggests that reduced glucose metabolism is only partially due to reduced glucose delivery [105].

The relevance of this finding is that the survival switch suppresses ATP production with a focus on reducing energy demands at rest but not when active (foraging) [19]. If the system is analogous to the brain, one would also expect that fructose might similarly lower resting brain ATP levels but retain the capacity to increase brain ATP levels in response to challenging tasks. Furthermore, reducing glucose

metabolism with high levels of glucose present owing to reduced metabolism would allow plenty of substrate for fructose generation via the polyol pathway.

Cerebral glucose hypometabolism in AD is also associated with changes in energetics and mitochondrial metabolism. Astrocytes, which normally generate two-thirds of their ATP equivalents via glycolysis [118], show reduced glycolysis with decreased lactate production [51] and progressive senescence [119]. Neurons also reduce ATP production owing to a decrease in OXPHOS [51]. This also occurs in aging [120, 121]. Neurons may produce some energy through glycolysis (at least in aging) because lactate uptake from neighboring astrocytes may be impaired because of a reduction in lactate transporters (monocarboxylate transporter proteins) in the neurons [122].

Oxidative stress is also increased in AD, as noted by the accumulation of malondialdehyde [123], and is associated with mitochondrial oxidative stress and mitochondrial loss [124]. Microglia are also converted from M2 macrophage-type cells (that use mitochondrial OXPHOS) to inflammatory M1-type macrophages that use glycolysis [47], thereby contributing to local neuroinflammation [125]. Interestingly, peripheral white cells in patients with AD show reduced aconitase, which would reduce the activity of the citric acid cycle critical for ATP production [126]. A reduction in aconitase is a characteristic consequence of fructose metabolism [15, 31].

The administration of fructose to laboratory animals can also induce similar changes in the brain, as observed in early AD (Table 2). For example, both fructose [127–129] and fructose-containing sugars [130, 131] can induce an impairment of spatial memory. Rats administered with fructose in drinking water for 8 wk developed hippocampal atrophy with reduced glucose uptake, decreased expression of phosphorylated IR-A and insulin receptor substrate-1, mitochondrial dysfunction, oxidative stress with stimulation of NF-κB and inflammatory cytokines, and a decrease in ATP compared with rats receiving regular water [131]. Giving fructose in the drinking water (10%) for a longer time (16–18 wk) model of AD resulted in obesity, decreased spatial memory, increased locomotor activity, cerebral insulin resistance (with low phosphoinositide 3-kinase (PI3K) activity and protein kinase B (Akt) levels), increased glycogen synthase kinase 3 beta (GSK3β) expression, lower acetylcholine content, and the accumulation of tau protein containing neurofilaments and Aβ amyloid plaques in the hippocampus compared with rats given regular water [132–134]. Administration of high doses of fructose to rats is also associated with greater mortality after stroke and is associated with a loss of astrocytes, greater neuroinflammation with hyperphosphorylation of tau protein [135], and hippocampal gliosis [136]. Fructose administration is also associated with more β-amyloid deposition in other animal models of AD [137, 138]. In all of these studies, the control groups were animals on regular chow.

Fructose has also been reported to directly inhibit mitochondrial OXPHOS in neurons and lead to neuron toxicity [139]. Similarly, directly injecting fructose into the hypothalamus causes local ATP depletion [140]. There is also evidence that astrocytes can be affected by fructose. In one study, pregnant mice were given fructose, and astrocytes were isolated from the infant mice. These astrocytes showed suppressed expression of the GLUT1 transporters, decreased glucose uptake, decreased glycolysis, decreased lactate generation, reduced glycogen stores, and decreased mitochondrial OXPHOS and mitochondrial biogenesis [141].

As mentioned earlier in the article, fructose may induce metabolic effects as a consequence of increasing uric acid levels in the brain. Hyperuricemic rats also develop memory defects (as demonstrated

with the Morris water maze) associated with increased hippocampal uric acid levels and local inflammation [68, 69]. Inflammation in the hippocampus can also be achieved by stereotactic infusion of uric acid [68] and is associated with hippocampal gliosis on MRI, and similar findings can be observed in hyperuricemic subjects [68]. The ability of uric acid to induce inflammation in the hippocampus is also consistent with a study showing that uric acid induces oxidative stress in neuronal-derived cells [142].

Other supporting data

Apolipoprotein E4 polymorphism

Apolipoprotein E4 (ApoE4) polymorphism is a major risk factor for AD, raising the question of how it relates to the fructose hypothesis. Notably, ApoE4 carriers show reduced cerebral glucose metabolism by positron emission testing and reduced uptake of glucose into astrocytes [143]. ApoE4-derived astrocytes also show enhanced glycolysis despite less mitochondrial OXPHOS and worse mitochondrial dysfunction compared with that with ApoE2 or ApoE3 astrocytes [143]. The relative similarities in the effects of fructose on the brain to that observed with the ApoE4 polymorphism suggest parallel pathogenic mechanisms.

Species specificity of AD

AD is relatively specific to humans, and although some primates show evidence of β -amyloid deposition in the brain, aggregated tau proteins are absent [144]. However, hibernating ground squirrels have been observed to have paired helical filaments (neurofibrillary tangles) of phosphorylated tau protein in the brain during hibernation, and this is reversible after arousal in the spring [145]. Given the observed associations of fructose [135] and uric acid [100] with tau-protein accumulation, it raises the possibility that the tau protein could be a response that initially provides some protection during hypoxia.

Studies on brain insulin receptors in knockout mice

Our hypothesis suggests that fructose blocks brain glucose metabolism to aid survival by reducing total energy needs, stimulating effective foraging and increasing weight; however, if severe and prolonged, fructose metabolism would lead to brain atrophy and possible dementia. Thus, it is of interest that blocking insulin signaling in the brain can extend the life span of *Drosophila* and *Caenorhabditis elegans*. For example, selectively knocking out insulin receptor substrate-2 (Irs2) in the brain of mice extends life span coupled with the development of obesity and insulin resistance [146]. However, knockout mice have a reduced brain size (30%). In contrast, heterozygous mice lacking Irs2 live longer than normal mice but still develop metabolic complications; however, they do not have a reduced brain size [146].

Challenges and Limitations

If uric acid is important in driving AD, why is it low in patients with AD?

Numerous studies have reported that subjects with AD have low serum uric acid levels, suggesting that this might be important to the pathogenesis [147]. However, although serum uric acid may reflect fructose metabolism, it also is a general marker of nutrition status [148]. Clinical manifestations of AD are often preceded by significant weight loss [125, 149, 150], which may account for the lower serum uric acid

levels on presentation of AD. This may also explain why obesity predicts AD in midlife but actually protects from AD late in life [151].

Some individuals with AD also lose excessive amounts of uric acid in their urine because of a defect in the proximal tubule. In one study of 18 randomly selected individuals with AD, one-third had abnormally high urate excretion (defined as a fractional excretion of uric acid of >10%) [152]. Interestingly, this finding may reflect the activation of the polyol-fructose pathway in the kidneys [153, 154].

Serum uric acid may also not reflect intracellular or brain uric acid levels. For example, certain foods, such as salt, will increase liver uric acid levels that reduce hepatic ATP levels despite no change in serum uric acid [14].

One way to resolve the controversial epidemiological data on whether uric acid is associated with increased [155, 156] or lower risk [157] of AD is to evaluate the effect of lowering uric acid levels on incident dementia. Here, studies found that uric acid–lowering therapy reduced the risk of dementia compared with that in subjects with untreated gout [158–160]. In one study, the use of febuxostat (a xanthine oxidase inhibitor) reduced the risk of dementia by 80% [160]. Another study reported a dose-dependent relationship, with higher doses of allopurinol and febuxostat providing greater protection [161].

What about the evidence that uric acid is an antioxidant?

Uric acid can function as an antioxidant and block peroxynitrite [162]. This observation has suggested that uric acid might be beneficial, especially in Parkinson's disease and multiple sclerosis. However, clinical trials in which serum uric acid was raised by administering inosine were negative in both diseases [163, 164]. Furthermore, the use of inosine is problematic because although it increases serum uric acid, it can enter the purine salvage pathway to stimulate ATP production [165]. Some investigators have administered allopurinol with inosine to block uric acid formation because this encourages more of the inosine to be used to increase ATP levels, and some preliminary studies suggest a benefit of this approach in Parkinson's disease (166).

If AD is driven by fructose, should AD have increased in parallel with obesity and diabetes?

Given that the risk for AD is increased by Western diets, obesity, and diabetes, one might predict that the sporadic (nonfamilial) form of AD should have increased dramatically during the 20th century. Unfortunately, there are no good data to determine whether this is the case. Although AD was reported infrequently in the early 20th century, it was initially thought to be distinct from “senile” dementia. Nevertheless, there is evidence from insurance companies, such as Blue Cross/Blue Shield, that early-onset AD increased dramatically between 2013 and 2017 (167). Today, AD affects 10% of subjects aged >65 y in USA (168).

Summary and Future Treatment Options

Here, we suggest that the effects of fructose on the brain were originally to stimulate foraging and reduce cerebral energy demands. Although the pathway was meant to be beneficial, the mutation in uricase amplified the switch, and the introduction of the Western diet provided ample fuel to put it in high gear, with the attempt to conserve energy resulting in a severe reduction in the energy required to maintain the needs of the neurons. Indeed, the wandering response, which is very

common in AD (169), may signify a persistent foraging response despite massive neuronal loss.

Although available data support our hypothesis(es), further studies are needed, particularly with a focus on individuals at risk, individuals with MCI, and subjects with early AD. Treatment trials that interrupt the pathway, including nutraceuticals, drugs that are currently available [132–134, 160], and future therapeutics, represent an important opportunity. Given that the fructose hypothesis can provide a complete pathway from inception to end-stage AD, there is a compelling need for further investigation into the role of fructose and diet in this condition.

Author contribution

The authors' responsibilities were as follows – RJJ wrote the first draft; DRT, DB, MN, LGS-L, MF, SB, MAL, DP: assisted in the editing of the manuscript; and all authors: read and approved the final manuscript. RJJ, DRT, LGS-L, and MAL have equity with Colorado Research Partners LLC, and RJJ has stock with XORTX Therapeutics. RJJ has received honoraria from Horizon Pharmaceuticals. DB is a consultant for Apollo Health and Life Seasons. All other authors report no conflict of interest.

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