The American Journal of Clinical Nutrition 117 (2023) 455–466

The American Journal of CLINICAL NUTRITION

journal homepage: www.journals.elsevier.com/the-american-journal-of-clinical-nutrition

Narrative Review

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

Richard J. Johnson [1,2,*], Dean R. Tolan [3], Dale Bredesen [4], Maria Nagel [5], Laura G. Sánchez-Lozada [6], Mehdi Fini [2], Scott Burtis [7], Miguel A. Lanaspa [2], David Perlmutter [8]

[1] *Department of Medicine, Rocky Mountain VA Medical Center, Aurora, CO, USA;* [2] *Department of Medicine, University of Colorado Anschutz Medical Center, Aurora, CO, USA;* [3] *Biology Department, Boston University, Boston, MA, USA;* [4] *Department of Molecular and Medical Pharmacology, David Geffen School of Medicine, University of California, Los Angeles, CA, USA;* [5] *Department of Neurology, University of Colorado Anschutz Medical Center, Aurora, CO, USA;* [6] *Department of Cardio-Renal Physiopathology, National Institute of Cardiology Ignacio Chávez, Mexico City, Mexico;* [7] *Burtis Chiropractic Center, Fairmont, MN, USA;* [8] *University of Miami Miller School of Medicine, Miami, FL, USA*

A B S T R A C T

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; CMRglc, cerebral metabolic rate for glucose; CSF, cerebral spinal fluid; FDG-PET, [^{18}F]-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.

* Corresponding author.
E-mail address: Richard.johnson@cuanschutz.edu (R.J. Johnson).

https://doi.org/10.1016/j.ajcnut.2023.01.002
Received 13 September 2022; Received in revised form 21 December 2022; Accepted 4 January 2023
Available online 11 January 2023
0002-9165/Published by Elsevier Inc. on behalf of American Society for Nutrition.

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 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.

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	Raise blood pressure
	Increase salt absorption in the gut and salt reabsorption by the kidneys	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.

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

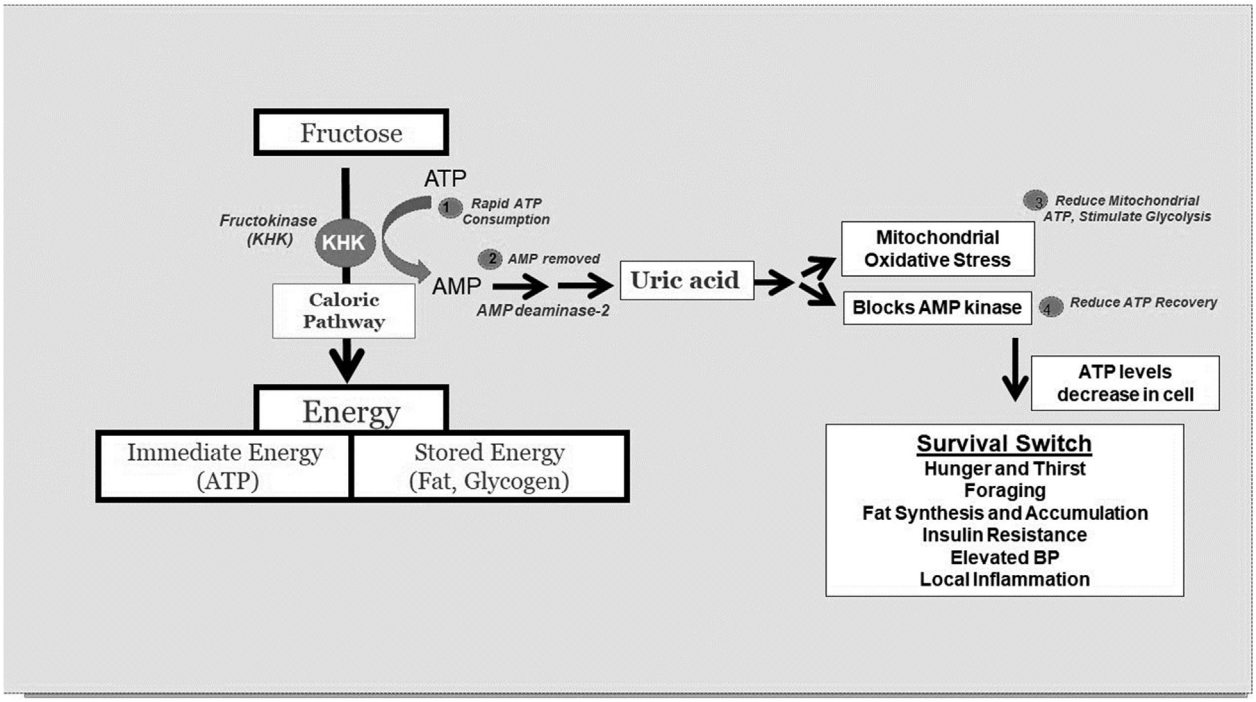

FIGURE 1. The fructose survival pathway. Fructose is metabolized by fructokinase to generate fructose-1-phosphate, which is then metabolized like any caloric sugar. However, the initial phosphorylation is associated with rapid ATP consumption with a decrease in intracellular phosphate that uniquely activates AMP deaminase-2, which subsequently removes AMP to generate uric acid. In turn, uric acid translocatess 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.

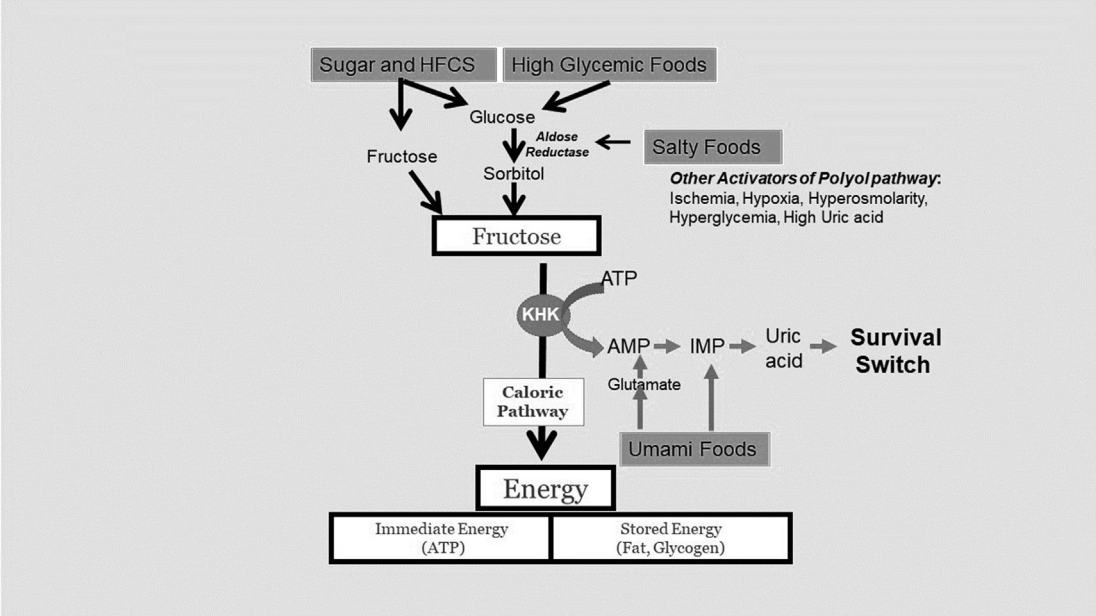

FIGURE 2. The process by which foods and stress engage the fructose survival pathway. Fructose can come directly from the diet (such as added sugars containing sucrose or high-fructose corn syrup [HFCS]) or from high glycemic carbohydrates. The latter provides excess glucose that can be converted via 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 Aβ amyloid by increasing glycolytic activity; however, if glycolysis is blocked, astrocytes develop reactive gliosis and die by apoptosis while Aβ 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 sensomotor 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 ishemia 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 postmortem 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

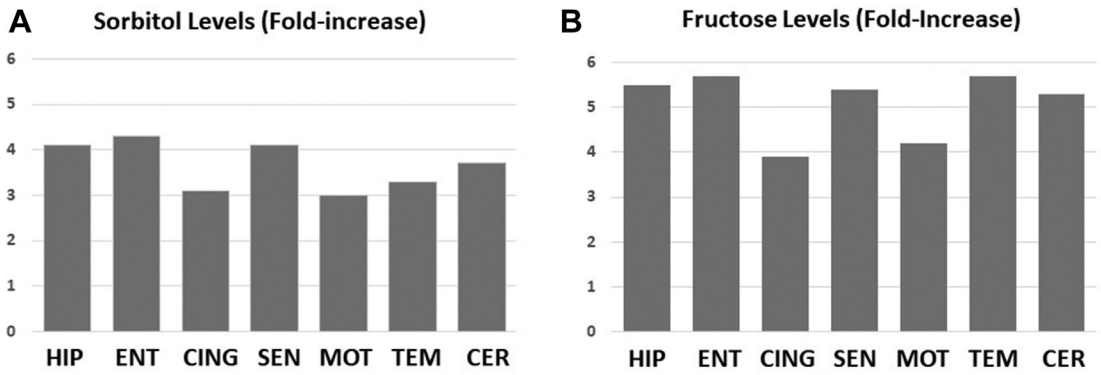

FIGURE 3. Evidence for activation the polyol pathway in the brains of patients with Alzheimer's disease. The endogenous production of fructose can only occur from the conversion of glucose to sorbitol and then to fructose via the polyol pathway. One study found ~4–5-fold higher levels of both sorbitol (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 [^{18}F]-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 assoviated 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.

Funding

This work was supported by VA Merit BXI01BX004511 from the Veterans Health Administration

References

[1] C.K. Kim, Y.R. Lee, L. Ong, M. Gold, A. Kalali, J. Sarkar, Alzheimer's disease: key insights from two decades of clinical trial failures, J Alzheimers Dis 87 (1) (2022) 83–100.

[2] S. Hoyer, Brain glucose and energy metabolism abnormalities in sporadic Alzheimer disease. Causes and consequences: an update, Exp Gerontol 35 (9–10) (2000) 1363–1372.

[3] R.V. Rao, S. Kumar, J. Gregory, C. Coward, S. Okada, W. Lipa, et al., ReCODE: a personalized, targeted, multi-factorial therapeutic program for reversal of cognitive decline, Biomedicines 9 (10) (2021) 1348.

[4] D. Perlmutter, K. Loberg, Grain brain: the surprising truth about wheat, carbs, and sugar—your brain's silent killers, Little, Brown and Company, New York, 2013.

[5] S. Craft, A. Claxton, L.D. Baker, A.J. Hanson, B. Cholerton, E.H. Trittschuh, et al., Effects of regular and long-acting insulin on cognition and Alzheimer's disease biomarkers: a pilot clinical trial, J Alzheimers Dis 57 (4) (2017) 1325–1334.

[6] R.J. Johnson, F. Gomez-Pinilla, M. Nagel, T. Nakagawa, B. Rodriguez-Iturbe, L.G. Sanchez-Lozada, et al., Cerebral fructose metabolism as a potential mechanism driving Alzheimer's disease, Front Aging Neurosci 12 (2020), 560865.

[7] G. Cahill Jr., P. Felig, O. Owen, J. Wahren, Metabolic adaptation to prolonged starvation in man, Nord Med 83 (3) (1970) 89.

[8] R.J. Johnson, P. Stenvinkel, P. Andrews, L.G. Sánchez-Lozada, T. Nakagawa, E. Gaucher, et al., Fructose metabolism as a common evolutionary pathway of survival associated with climate change, food shortage and droughts, J Intern Med 287 (3) (2020) 252–262.

[9] R.J. Johnson, L.G. Sánchez Lozada, T. Nakagawa, B. Rodriguez-Iturbe, D.R. Tolan, E.A. Gaucher, et al., Do thrifty genes exist? Revisiting uricase, Obesity (Silver Spring) 30 (10) (2022) 1917–1926.

[10] V.S. Malik, F.B. Hu, The role of sugar-sweetened beverages in the global epidemics of obesity and chronic diseases, Nat Rev Endocrinol 18 (4) (2022) 205–218.

[11] T. Nakagawa, H. Hu, S. Zharikov, K.R. Tuttle, R.A. Short, O. Glushakova, et al., A causal role for uric acid in fructose-induced metabolic syndrome, Am J Physiol Renal Physiol 290 (3) (2006) F625–F631.

[12] K.L. Stanhope, J.M. Schwarz, N.L. Keim, S.C. Griffen, A.A. Bremer, J.L. Graham, et al., Consuming fructose-sweetened, not glucose-sweetened, beverages increases visceral adiposity and lipids and decreases insulin sensitivity in overweight/obese humans, J Clin Invest 119 (5) (2009 May) 1322–1334, https://doi.org/10.1172/JCI37385. Epub 2009 Apr 20. PMID: 19381015; PMCID: PMC2673878.

[13] R.J. Johnson, M.S. Segal, Y. Sautin, T. Nakagawa, D.I. Feig, D.H. Kang, et al., Potential role of sugar (fructose) in the epidemic of hypertension, obesity and the metabolic syndrome, diabetes, kidney disease, and cardiovascular disease, Am J Clin Nutr 86 (4) (2007) 899–906.

[14] M.A. Lanaspa, M. Kuwabara, A. Andres-Hernando, N. Li, C. Cicerchi, T. Jensen, et al., High salt intake causes leptin resistance and obesity in mice by stimulating endogenous fructose production and metabolism, Proc Natl Acad Sci U S A 115 (12) (2018) 3138–3143.

[15] M.A. Lanaspa, L.G. Sanchez-Lozada, Y.J. Choi, C. Cicerchi, M. Kanbay, C.A. Roncal-Jimenez, et al., Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver, J Biol Chem 287 (48) (2012) 40732–40744.

[16] A. Andres-Hernando, T.J. Jensen, M. Kuwabara, D.J. Orlicky, C. Cicerchi, N. Li, et al., Vasopressin mediates fructose-induced metabolic syndrome by activating the V1b receptor, JCI Insight 6 (1) (2021), e140848.

[17] A. Andres-Hernando, D.J. Orlicky, M. Kuwabara, T. Ishimoto, T. Nakagawa, R.J. Johnson, et al., Deletion of fructokinase in the liver or in the intestine reveals differential effects on sugar-induced metabolic dysfunction, Cell Metab 32 (1) (2020) 117, 27.e3.

[18] Z. Song, C.A. Roncal-Jimenez, M.A. Lanaspa-Garcia, S.A. Oppelt, M. Kuwabara, T. Jensen, et al., Role of fructose and fructokinase in acute dehydration-induced vasopressin gene expression and secretion in mice, J Neurophysiol 117 (2) (2017) 646–654.

[19] C.L. Cox, K.L. Stanhope, J.M. Schwarz, J.L. Graham, B. Hatcher, S.C. Griffen, et al., Consumption of fructose-sweetened beverages for 10 weeks reduces net fat oxidation and energy expenditure in overweight/obese men and women, Eur J Clin Nutr 66 (2) (2012) 201–208.

[20] J. Franco-Peréz, J. Manjarrez-Marmolejo, P. Ballesteros-Zebadúa, A. Neri-Santos, S. Montes, N. Suarez-Rivera, et al., Chronic consumption of fructose induces behavioral alterations by increasing orexin and dopamine levels in the rat brain, Nutrients 10 (11) (2018) 1722.

[21] A. Shapiro, W. Mu, C. Roncal, K.Y. Cheng, R.J. Johnson, P.J. Scarpace, Fructose-induced leptin resistance exacerbates weight gain in response to subsequent high-fat feeding, Am J Physiol Regul Integr Comp Physiol 295 (5) (2008) R1370–R1375.

[22] R.J. Johnson, W.L. Wilson, S.T. Bland, M.A. Lanaspa, Fructose and uric acid as drivers of a hyperactive foraging response: a clue to behavioral disorders associated with impulsivity or mania? Evol Hum Behav 42 (3) (2021) 194–203.

[23] T.J. Park, J. Reznick, B.L. Peterson, G. Blass, D. Omerbašić, N.C. Bennett, et al., Fructose-driven glycolysis supports anoxia resistance in the naked mole-rat, Science 356 (6335) (2017) 307–311.

[24] T. Nakagawa, M.A. Lanaspa, I.S. Millan, M. Fini, C.J. Rivard, L.G. Sanchez-Lozada, et al., Fructose contributes to the Warburg effect for cancer growth, Cancer Metab 8 (2020) 16.

[25] M.A. Lanaspa, C. Cicerchi, G. Garcia, N. Li, C.A. Roncal-Jimenez, C.J. Rivard, et al., Counteracting roles of AMP deaminase and AMP kinase in the development of fatty liver, PLoS One 7 (11) (2012), e48801.

[26] J.H. Youn, H.R. Kaslow, R.N. Bergman, Fructose effect to suppress hepatic glycogen degradation, J Biol Chem 262 (24) (1987) 11470–11477.

[27] Y. Zhu, Y. Hu, T. Huang, Y. Zhang, Z. Li, C. Luo, et al., High uric acid directly inhibits insulin signalling and induces insulin resistance, Biochem Biophys Res Commun 447 (4) (2014) 707–714.

[28] S. Softic, K.L. Stanhope, J. Boucher, S. Divanovic, M.A. Lanaspa, R.J. Johnson, et al., Fructose and hepatic insulin resistance, Crit Rev Clin Lab Sci 57 (5) (2020) 308–322.

[29] R.J. Johnson, P. Stenvinkel, T. Jensen, M.A. Lanaspa, C. Roncal, Z. Song, et al., Metabolic and kidney diseases in the setting of climate change, water shortage, and survival factors, J Am Soc Nephrol 27 (8) (2016) 2247–2256.

[30] P.H. Mäenpää, K.O. Raivio, M.P. Kekomäki, Liver adenine nucleotides: fructose-induced depletion and its effect on protein synthesis, Science 161 (3847) (1968) 1253–1254.

[31] L.G. Sánchez-Lozada, M.A. Lanaspa, M. Cristóbal-Garcia, F. García-Arroyo, V. Soto, D. Cruz-Robles, et al., Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations, Nephron Exp Nephrol 121 (3–4) (2012) e71–e78.

[32] P. Mirtschink, W. Krek, Hypoxia-driven glycolytic and fructolytic metabolic programs: pivotal to hypertrophic heart disease, Biochim Biophys Acta 1863 (7 Pt B) (2016) 1822–1828.

[33] R.J. Johnson, P. Stenvinkel, S.L. Martin, A. Jani, L.G. Sánchez-Lozada, J.O. Hill, et al., Redefining metabolic syndrome as a fat storage condition based on studies of comparative physiology, Obesity (Silver Spring) 21 (4) (2013) 659–664.

[34] B. Ruepp, K.M. Bohren, K.H. Gabbay, Characterization of the osmotic response element of the human aldose reductase gene promoter, Proc Natl Acad Sci U S A 93 (16) (1996) 8624–8629.

[35] Y.C. Hwang, M. Kaneko, S. Bakr, H. Liao, Y. Lu, E.R. Lewis, et al., Central role for aldose reductase pathway in myocardial ischemic injury, FASEB J 18 (11) (2004) 1192–1199.
[36] L.G. Sanchez-Lozada, A. Andres-Hernando, F.E. Garcia-Arroyo, C. Cicerchi, N. Li, M. Kuwabara, et al., Uric acid activates aldose reductase and the polyol pathway for endogenous fructose and fat production causing development of fatty liver in rats, J Biol Chem 294 (11) (2019) 4272–4281.
[37] A. Andres-Hernando, N. Li, C. Cicerchi, S. Inaba, W. Chen, C. Roncal-Jimenez, et al., Protective role of fructokinase blockade in the pathogenesis of acute kidney injury in mice, Nat Commun 8 (2017), 14181.
[38] I.H. Fox, T.D. Palella, W.N. Kelley, Hyperuricemia: a marker for cell energy crisis, N Engl J Med 317 (2) (1987) 111–112.
[39] M.A. Lanaspa, T. Ishimoto, N. Li, C. Cicerchi, D.J. Orlicky, P. Ruzycki, et al., Endogenous fructose production and metabolism in the liver contributes to the development of metabolic syndrome, Nat Commun 4 (2013) 2434.
[40] A. Andres-Hernando, C. Cicerchi, M. Kuwabara, D.J. Orlicky, L.G. Sanchez-Lozada, T. Nakagawa, et al., Umami-induced obesity and metabolic syndrome is mediated by nucleotide degradation and uric acid generation, Nat Metab 3 (9) (2021) 1189–1201.
[41] C. Francey, J. Cros, R. Rosset, C. Crézé, V. Rey, N. Stefanoni, et al., The extra-splanchnic fructose escape after ingestion of a fructose-glucose drink: an exploratory study in healthy humans using a dual fructose isotope method, Clin Nutr ESPEN 29 (2019) 125–132.
[42] A. Andres-Hernando, M. Kuwabara, D.J. Orlicky, A. Vandenbeuch, C. Cicerchi, S.C. Kinnamon, et al., Sugar causes obesity and metabolic syndrome in mice independently of sweet taste, Am J Physiol Endocrinol Metab 319 (2) (2020) E276–E290.
[43] J.T. Kratzer, M.A. Lanaspa, M.N. Murphy, C. Cicerchi, C.L. Graves, P.A. Tipton, et al., Evolutionary history and metabolic insights of ancient mammalian uricases, Proc Natl Acad Sci U S A 111 (10) (2014) 3763–3768.
[44] E. Tapia, M. Cristóbal, F.E. García-Arroyo, V. Soto, F. Monroy-Sánchez, U. Pacheco, et al., Synergistic effect of uricase blockade plus physiological amounts of fructose-glucose on glomerular hypertension and oxidative stress in rats, Am J Physiol Renal Physiol 304 (6) (2013) F727–F736.
[45] G. Sundborn, S. Thornley, T.R. Merriman, B. Lang, C. King, M.A. Lanaspa, et al., Are liquid sugars different from solid sugar in their ability to cause metabolic syndrome? Obesity (Silver Spring) 27 (6) (2019) 879–887.
[46] C. Jang, S. Hui, W. Lu, A.J. Cowan, R.J. Morscher, G. Lee, et al., The small intestine converts dietary fructose into glucose and organic acids, Cell Metab 27 (2) (2018) 351, 61.e3.
[47] Q. Wang, L. Duan, X. Li, Y. Wang, W. Guo, F. Guan, et al., Glucose metabolism, neural cell senescence and Alzheimer's disease, Int J Mol Sci 23 (8) (2022) 4351.
[48] M. Bélanger, I. Allaman, P.J. Magistretti, Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation, Cell Metab 14 (6) (2011) 724–738.
[49] P. Schönfeld, G. Reiser, Why does brain metabolism not favor burning of fatty acids to provide energy? Reflections on disadvantages of the use of free fatty acids as fuel for brain, J Cereb Blood Flow Metab 33 (10) (2013) 1493–1499.
[50] E.C. McNay, J. Pearson-Leary, GluT4: a central player in hippocampal memory and brain insulin resistance, Exp Neurol 323 (2020), 113076.
[51] E. Beard, S. Lengacher, S. Dias, P.J. Magistretti, C. Finsterwald, Astrocytes as key regulators of brain energy metabolism: new therapeutic perspectives, Front Physiol 12 (2021), 825816.
[52] A.B. Walls, C.M. Heimbürger, S.D. Bouman, A. Schousboe, H.S. Waagepetersen, Robust glycogen shunt activity in astrocytes: effects of glutamatergic and adrenergic agents, Neuroscience 158 (1) (2009) 284–292.
[53] G.F. Cahill Jr., Fuel metabolism in starvation, Annu Rev Nutr 26 (2006) 1–22.
[54] S.P. Allen, R.S. Seehra, P.R. Heath, B.P.C. Hall, J. Bates, C.J. Garwood, et al., Transcriptomic analysis of human astrocytes in vitro reveals hypoxia-induced mitochondrial dysfunction, modulation of metabolism, and dysregulation of the immune response, Int J Mol Sci 21 (21) (2020) 8028.
[55] W. Fu, D. Shi, D. Westaway, J.H. Jhamandas, Bioenergetic mechanisms in astrocytes may contribute to amyloid plaque deposition and toxicity, J Biol Chem 290 (20) (2015) 12504–12513.
[56] B.Y. Hayden, J.M. Pearson, M.L. Platt, Neuronal basis of sequential foraging decisions in a patchy environment, Nat Neurosci 14 (7) (2011) 933–939.
[57] N. Kolling, T.E. Behrens, R.B. Mars, M.F. Rushworth, Neural mechanisms of foraging, Science 336 (6077) (2012) 95–98.
[58] R.U. Pliquett, D. Führer, S. Falk, S. Zysset, D.Y. von Cramon, M. Stumvoll, The effects of insulin on the central nervous system—focus on appetite regulation, Horm Metab Res 38 (7) (2006) 442–446.
[59] D.L. Barack, S.W.C. Chang, M.L. Platt, Posterior cingulate neurons dynamically signal decisions to disengage during foraging, Neuron 96 (2) (2017) 339, 47.e5.
[60] R. Leech, D.J. Sharp, The role of the posterior cingulate cortex in cognition and disease, Brain 137 (1) (2014) 12–32.
[61] K.A. Page, O. Chan, J. Arora, R. Belfort-Deaguiar, J. Dzuira, B. Roehmholdt, et al., Effects of fructose vs glucose on regional cerebral blood flow in brain regions involved with appetite and reward pathways, JAMA 309 (1) (2013) 63–70.
[62] J.Q. Purnell, B.A. Klopfenstein, A.A. Stevens, P.J. Havel, S.H. Adams, T.N. Dunn, et al., Brain functional magnetic resonance imaging response to glucose and fructose infusions in humans, Diabetes Obes Metab 13 (3) (2011) 229–234.
[63] S. Luo, J.R. Monterosso, K. Sarpelleh, K.A. Page, Differential effects of fructose versus glucose on brain and appetitive responses to food cues and decisions for food rewards, Proc Natl Acad Sci U S A 112 (20) (2015) 6509–6514.
[64] R.A. Gelfand, R.S. Sherwin, Nitrogen conservation in starvation revisited: protein sparing with intravenous fructose, Metabolism 35 (1) (1986) 37–44.
[65] J.J. Hwang, L. Jiang, M. Hamza, F. Dai, R. Belfort-DeAguiar, G. Cline, et al., The human brain produces fructose from glucose, JCI Insight 2 (4) (2017), e90508.
[66] A. Brun, L. Gustafson, Distribution of cerebral degeneration in Alzheimer's disease. A clinico-pathological study, Arch Psychiatr Nervenkr 223 (1) (1976) 15–33, 1970.
[67] W.H. Oldendorf, Brain uptake of radiolabeled amino acids, amines, and hexoses after arterial injection, Am J Physiol 221 (6) (1971) 1629–1639.
[68] X. Shao, W. Lu, F. Gao, D. Li, J. Hu, Y. Li, et al., Uric acid induces cognitive dysfunction through hippocampal inflammation in rodents and humans, J Neurosci 36 (43) (2016) 10990–11005.
[69] C. Shi, H. Guo, X. Liu, High uric acid induced hippocampal mitochondrial dysfunction and cognitive impairment involving intramitochondrial NF-κB inhibitor α/nuclear factor-κB pathway, Neuroreport 33 (3) (2022) 109–115.
[70] M.A. Lanaspa, L.G. Sanchez-Lozada, C. Cicerchi, N. Li, C.A. Roncal-Jimenez, T. Ishimoto, et al., Uric acid stimulates fructokinase and accelerates fructose metabolism in the development of fatty liver, PLoS One 7 (10) (2012), e47948.
[71] S.A. Oppelt, W. Zhang, D.R. Tolan, Specific regions of the brain are capable of fructose metabolism, Brain Res 1657 (2017) 312–322.
[72] B. Sims, R.E. Powers, R.L. Sabina, A.B. Theibert, Elevated adenosine monophosphate deaminase activity in Alzheimer's disease brain, Neurobiol Aging 19 (5) (1998) 385–391.
[73] M.D. Lane, S.H. Cha, Effect of glucose and fructose on food intake via malonyl-CoA signaling in the brain, Biochem Biophys Res Commun 382 (1) (2009) 1–5.
[74] C.P. Diggle, M. Shires, D. Leitch, D. Brooke, I.M. Carr, A.F. Markham, et al., Ketohexokinase: expression and localization of the principal fructose-metabolizing enzyme, J Histochem Cytochem 57 (8) (2009) 763–774.
[75] E.E. Penhoet, W.J. Rutter, Catalytic and immunochemical properties of homomeric and heteromeric combinations of aldolase subunits, J Biol Chem 246 (2) (1971) 318–323.
[76] P.I. Moreira, High-sugar diets, type 2 diabetes and Alzheimer's disease, Curr Opin Clin Nutr Metab Care 16 (4) (2013) 440–445.
[77] G.E. Crichton, M.F. Elias, R.V. Torres, Sugar-sweetened soft drinks are associated with poorer cognitive function in individuals with type 2 diabetes: the Maine-Syracuse Longitudinal Study, Br J Nutr 115 (8) (2016) 1397–1405.
[78] M.K. Taylor, D.K. Sullivan, R.H. Swerdlow, E.D. Vidoni, J.K. Morris, J.D. Mahnken, et al., A high-glycemic diet is associated with cerebral amyloid burden in cognitively normal older adults, Am J Clin Nutr 106 (6) (2017) 1463–1470.
[79] R.O. Roberts, L.A. Roberts, Y.E. Geda, R.H. Cha, V.S. Pankratz, H.M. O'Connor, et al., Relative intake of macronutrients impacts risk of mild cognitive impairment or dementia, J Alzheimers Dis 32 (2) (2012) 329–339.
[80] D. Mohan, K.H. Yap, D. Reidpath, Y.C. Soh, A. McGrattan, B.C.M. Stephan, et al., Link between dietary sodium intake, cognitive function, and dementia risk in middle-aged and older adults: a systematic review, J Alzheimers Dis 76 (4) (2020) 1347–1373.
[81] A.J. Fiocco, B. Shatenstein, G. Ferland, H. Payette, S. Belleville, M.J. Kergoat, et al., Sodium intake and physical activity impact cognitive maintenance in older adults: the NuAge Study, Neurobiol Aging 33 (4) (2012) 829, e21–8.
[82] A. Venkataraman, N. Kalk, G. Sewell, C.W. Ritchie, A. Lingford-Hughes, Alcohol and Alzheimer's disease-does alcohol dependence contribute to beta-amyloid deposition, neuroinflammation and neurodegeneration in Alzheimer's disease? Alcohol Alcohol 52 (2) (2017) 151–158.
[83] H. Zhang, D.C. Greenwood, H.A. Risch, D. Bunce, L.J. Hardie, J.E. Cade, Meat consumption and risk of incident dementia: cohort study of 493,888 UK Biobank participants, Am J Clin Nutr 114 (1) (2021) 175–184.

[84] V. Berti, J. Murray, M. Davies, N. Spector, W.H. Tsui, Y. Li, et al., Nutrient patterns and brain biomarkers of Alzheimer's disease in cognitively normal individuals, J Nutr Health Aging 19 (4) (2015) 413–423.
[85] M. Wang, W.Y. Chen, J. Zhang, L. Gobejishvili, S.S. Barve, C.J. McClain, et al., Elevated fructose and uric acid through aldose reductase contribute to experimental and human alcoholic liver disease, Hepatology 72 (5) (2020) 1617–1637.
[86] C.A. Roncal-Jimenez, T. Ishimoto, M.A. Lanaspa, T. Milagres, A.A. Hernando, T. Jensen, et al., Aging-associated renal disease in mice is fructokinase dependent, Am J Physiol Renal Physiol 311 (4) (2016) F722–F730.
[87] E. Cereda, M.C. Sacchi, A.E. Malavazos, Central obesity and increased risk of dementia more than three decades later, Neurology 72 (11) (2009) 1030–1031. ; author reply 1031.
[88] W.L. Xu, A.R. Atti, M. Gatz, N.L. Pedersen, B. Johansson, L. Fratiglioni, Midlife overweight and obesity increase late-life dementia risk: a population-based twin study, Neurology 76 (18) (2011) 1568–1574.
[89] V. Solfrizzi, E. Scafato, C. Capurso, A. D'Introno, A.M. Colacicco, V. Frisardi, et al., Metabolic syndrome, mild cognitive impairment, and progression to dementia. The Italian longitudinal study on aging, Neurobiol Aging 32 (11) (2011) 1932–1941.
[90] L. Kerti, A.V. Witte, A. Winkler, U. Grittner, D. Rujescu, A. Flöel, Higher glucose levels associated with lower memory and reduced hippocampal microstructure, Neurology 81 (20) (2013) 1746–1752.
[91] L.D. Baker, D.J. Cross, S. Minoshima, D. Belongia, G.S. Watson, S. Craft, Insulin resistance and Alzheimer-like reductions in regional cerebral glucose metabolism for cognitively normal adults with prediabetes or early type 2 diabetes, Arch Neurol 68 (1) (2011) 51–57.
[92] J.K. Morris, E.D. Vidoni, H.M. Wilkins, A.E. Archer, N.C. Burns, R.T. Karcher, et al., Impaired fasting glucose is associated with increased regional cerebral amyloid, Neurobiol Aging 44 (2016) 138–142.
[93] C.M. Burns, K. Chen, A.W. Kaszniak, W. Lee, G.E. Alexander, D. Bandy, et al., Higher serum glucose levels are associated with cerebral hypometabolism in Alzheimer regions, Neurology 80 (17) (2013) 1557–1564.
[94] Z. Arvanitakis, R.S. Wilson, J.L. Bienias, D.A. Evans, D.A. Bennett, Diabetes mellitus and risk of Alzheimer disease and decline in cognitive function, Arch Neurol 61 (5) (2004) 661–666.
[95] R.J. Zeman, X. Wen, N. Ouyang, A.M. Brown, J.D. Etlinger, Role of the polyol pathway in locomotor recovery and Wallerian degeneration after spinal cord contusion injury, Neurotrauma Rep 2 (1) (2021) 411–423.
[96] J. Xu, P. Begley, S.J. Church, S. Patassini, S. McHarg, N. Kureishy, et al., Elevation of brain glucose and polyol-pathway intermediates with accompanying brain-copper deficiency in patients with Alzheimer's disease: metabolic basis for dementia, Sci Rep 6 (2016), 27524.
[97] S. Hoyer, R. Nitsch, K. Oesterreich, Ammonia is endogenously generated in the brain in the presence of presumed and verified dementia of Alzheimer type, Neurosci Lett 117 (3) (1990) 358–362.
[98] S.Z. Sun, M.W. Empie, Fructose metabolism in humans - what isotopic tracer studies tell us, Nutr Metab (Lond). 9 (1) (2012) 89.
[99] S. Hoyer, K. Oesterreich, O. Wagner, Glucose metabolism as the site of the primary abnormality in early-onset dementia of Alzheimer type? J Neurol 235 (3) (1988) 143–148.
[100] R. Kaddurah-Daouk, H. Zhu, S. Sharma, M. Bogdanov, S.G. Rozen, W. Matson, et al., Alterations in metabolic pathways and networks in Alzheimer's disease, Transl Psychiatry 3 (2013) e244.
[101] S. Huang, J. Wang, D.Y. Fan, T. Luo, Y. Li, Y.F. Tu, et al., The association of serum uric acid with cognitive impairment and ATN biomarkers, Front Aging Neurosci 14 (2022), 943380.
[102] N.R. McFarland, T. Burdett, C.A. Desjardins, M.P. Frosch, M.A. Schwarzschild, Postmortem brain levels of urate and precursors in Parkinson's disease and related disorders, Neurodegener Dis 12 (4) (2013) 189–198.
[103] S. Hoyer, Oxidative energy metabolism in Alzheimer brain. Studies in early-onset and late-onset cases, Mol Chem Neuropathol 16 (3) (1992) 207–224.
[104] E. Al-Ozairi, C.J. Rivard, L.G. Sanchez-Lozada, M.A. Lanaspa, P. Bjornstad, D. Al Salem, et al., Fructose tolerance test in obese people with and without type 2 diabetes, J Diabetes 12 (3) (2020) 197–204.
[105] L. Mosconi, A. Pupi, M.J. De Leon, Brain glucose hypometabolism and oxidative stress in preclinical Alzheimer's disease, Ann N Y Acad Sci 1147 (2008) 180–195.
[106] S. Craft, The role of metabolic disorders in Alzheimer disease and vascular dementia: two roads converged, Arch Neurol 66 (3) (2009) 300–305.
[107] S.E. Arnold, Z. Arvanitakis, S.L. Macauley-Rambach, A.M. Koenig, H.Y. Wang, R.S. Ahima, et al., Brain insulin resistance in type 2 diabetes and Alzheimer disease: concepts and conundrums, Nat Rev Neurol 14 (3) (2018) 168–181.
[108] L. Mosconi, W.H. Tsui, H. Rusinek, S. De Santi, Y. Li, G.J. Wang, et al., Quantitation, regional vulnerability, and kinetic modeling of brain glucose metabolism in mild Alzheimer's disease, Eur J Nucl Med Mol Imaging 34 (9) (2007) 1467–1479.
[109] S. Hoyer, The brain insulin signal transduction system and sporadic (type II) Alzheimer disease: an update, J Neural Transm (Vienna) 109 (3) (2002) 341–360.
[110] L. Szablewski, Brain glucose transporters: role in pathogenesis and potential targets for the treatment of Alzheimer's disease, Int J Mol Sci 22 (15) (2021) 8142.
[111] Y. An, V.R. Varma, S. Varma, R. Casanova, E. Dammer, O. Pletnikova, et al., Evidence for brain glucose dysregulation in Alzheimer's disease, Alzheimers Dement 14 (3) (2018) 318–329.
[112] E.R. Seaquist, G.S. Damberg, I. Tkac, R. Gruetter, The effect of insulin on in vivo cerebral glucose concentrations and rates of glucose transport/metabolism in humans, Diabetes 50 (10) (2001) 2203–2209.
[113] S.M. Gray, R.I. Meijer, E.J. Barrett, Insulin regulates brain function, but how does it get there? Diabetes 63 (12) (2014) 3992–3997.
[114] B.J. Neth, S. Craft, Insulin resistance and Alzheimer's disease: bioenergetic linkages, Front Aging Neurosci 9 (2017) 345.
[115] S. Hoyer, The aging brain. Changes in the neuronal insulin/insulin receptor signal transduction cascade trigger late-onset sporadic Alzheimer disease (SAD). A mini-review, J Neural Transm (Vienna) 109 (7–8) (2002) 991–1002.
[116] N. Henneberg, S. Hoyer, Desensitization of the neuronal insulin receptor: a new approach in the etiopathogenesis of late-onset sporadic dementia of the Alzheimer type (SDAT)? Arch Gerontol Geriatr 21 (1) (1995) 63–74.
[117] S.I. Rapoport, C.L. Grady, Parametric in vivo brain imaging during activation to examine pathological mechanisms of functional failure in Alzheimer disease, Int J Neurosci 70 (1–2) (1993) 39–56.
[118] S.P. Allen, B. Hall, L.M. Castelli, L. Francis, R. Woof, A.P. Siskos, et al., Astrocyte adenosine deaminase loss increases motor neuron toxicity in amyotrophic lateral sclerosis, Brain 142 (3) (2019) 586–605.
[119] R. Bhat, E.P. Crowe, A. Bitto, M. Moh, C.D. Katsetos, F.U. Garcia, et al., Astrocyte senescence as a component of Alzheimer's disease, PLoS One 7 (9) (2012), e45069.
[120] D.G. Souza, B. Bellaver, G.S. Raupp, D.O. Souza, A. Quincozes-Santos, Astrocytes from adult Wistar rats aged in vitro show changes in glial functions, Neurochem Int 90 (2015) 93–97.
[121] M.S. Goyal, A.G. Vlassenko, T.M. Blazey, Y. Su, L.E. Couture, T.J. Durbin, et al., Loss of brain aerobic glycolysis in normal human aging, Cell Metab 26 (2) (2017) 353, 60.e3.
[122] D. Drulis-Fajdasz, A. Gizak, T. Wójtowicz, J.R. Wiśniewski, D. Rakus, Aging-associated changes in hippocampal glycogen metabolism in mice. Evidence for and against astrocyte-to-neuron lactate shuttle, Glia 66 (7) (2018) 1481–1495.
[123] M. Zabel, A. Nackenoff, W.M. Kirsch, F.E. Harrison, G. Perry, M. Schrag, Markers of oxidative damage to lipids, nucleic acids and proteins and antioxidant enzymes activities in Alzheimer's disease brain: a meta-analysis in human pathological specimens, Free Radic Biol Med 115 (2018) 351–360.
[124] J. Ojaimi, E. Byrne, Mitochondrial function and Alzheimer's disease, Biol Signals Recept 10 (3–4) (2001) 254–262.
[125] R. Stewart, K. Masaki, Q.L. Xue, R. Peila, H. Petrovitch, L.R. White, et al., A 32-year prospective study of change in body weight and incident dementia: the Honolulu-Asia Aging Study, Arch Neurol 62 (1) (2005) 55–60.
[126] D.J. Tyrrell, M.S. Bharadwaj, M.J. Jorgensen, T.C. Register, C. Shively, R.N. Andrews, et al., Blood-based bioenergetic profiling reflects differences in brain bioenergetics and metabolism, Oxid Med Cell Longev (2017), 7317251, 2017.
[127] P. Cisternas, P. Salazar, F.G. Serrano, C. Montecinos-Oliva, S.B. Arredondo, L. Varela-Nallar, et al., Fructose consumption reduces hippocampal synaptic plasticity underlying cognitive performance, Biochim Biophys Acta 1852 (11) (2015) 2379–2390.
[128] A. Jiménez-Maldonado, Z. Ying, H.R. Byun, F. Gomez-Pinilla, Short-term fructose ingestion affects the brain independently from establishment of metabolic syndrome, Biochim Biophys Acta Mol Basis Dis 1864 (1) (2018) 24–33.
[129] A.P. Ross, T.J. Bartness, J.G. Mielke, M.B. Parent, A high fructose diet impairs spatial memory in male rats, Neurobiol Learn Mem 92 (3) (2009) 410–416.
[130] M.D. Kendig, C.S. Lin, J.E. Beilharz, K.B. Rooney, R.A. Boakes, Maltodextrin can produce similar metabolic and cognitive effects to those of sucrose in the rat, Appetite 77 (2014) 1–12.

[131] R. Agrawal, E. Noble, L. Vergnes, Z. Ying, K. Reue, F. Gomez-Pinilla, Dietary fructose aggravates the pathobiology of traumatic brain injury by influencing energy homeostasis and plasticity, J Cereb Blood Flow Metab 36 (5) (2016) 941–953.
[132] H.E. Mohamed, M.E. Asker, M.A. Shaheen, R.G. Eissa, N.N. Younis, Alleviation of fructose-induced Alzheimer's disease in rats by pioglitazone and decaffeinated green coffee bean extract, J Food Biochem 45 (5) (2021), e13715.
[133] H.E. Mohamed, M.E. Asker, N.N. Younis, M.A. Shaheen, R.G. Eissa, Modulation of brain insulin signaling in Alzheimer's disease: new insight on the protective role of green coffee bean extract, Nutr Neurosci 23 (1) (2020) 27–36.
[134] D. Luo, X. Hou, L. Hou, M. Wang, S. Xu, C. Dong, et al., Effect of pioglitazone on altered expression of Abeta metabolism-associated molecules in the brain of fructose-drinking rats, a rodent model of insulin resistance, Eur J Pharmacol 664 (1–3) (2011) 14–19.
[135] P.A. Pérez-Corredor, J.A. Gutiérrez-Vargas, L. Ciro-Ramírez, N. Balcazar, G.P. Cardona-Gómez, High fructose diet-induced obesity worsens post-ischemic brain injury in the hippocampus of female rats, Nutr Neurosci 25 (1) (2022) 122–136.
[136] W.C. Liu, C.W. Wu, Y.L. Tain, M.H. Fu, C.Y. Hung, I.C. Chen, et al., Oral pioglitazone ameliorates fructose-induced peripheral insulin resistance and hippocampal gliosis but not restores inhibited hippocampal adult neurogenesis, Biochim Biophys Acta Mol Basis Dis 1864 (1) (2018) 274–285.
[137] S.H. Yeh, F.S. Shie, H.K. Liu, H.H. Yao, P.C. Kao, Y.H. Lee, et al., A high-sucrose diet aggravates Alzheimer's disease pathology, attenuates hypothalamic leptin signaling, and impairs food-anticipatory activity in APPswe/PS1dE9 mice, Neurobiol Aging 90 (2020) 60–74.
[138] D. Cao, H. Lu, T.L. Lewis, L. Li, Intake of sucrose-sweetened water induces insulin resistance and exacerbates memory deficits and amyloidosis in a transgenic mouse model of Alzheimer disease, J Biol Chem 282 (50) (2007) 36275–36282.
[139] D. Lodha, S. Rajasekaran, T. Jayavelu, J.R. Subramaniam, Detrimental effects of fructose on mitochondria in mouse motor neurons and on C. elegans healthspan, Nutr Neurosci 25 (6) (2022) 1277–1286.
[140] S.H. Cha, M. Wolfgang, Y. Tokutake, S. Chohnan, M.D. Lane, Differential effects of central fructose and glucose on hypothalamic malonyl-CoA and food intake, Proc Natl Acad Sci U S A 105 (44) (2008) 16871–16875.
[141] C.W. Wu, C.Y. Hung, H. Hirase, Y.L. Tain, W.C. Lee, J.Y.H. Chan, et al., Pioglitazone reversed the fructose-programmed astrocytic glycolysis and oxidative phosphorylation of female rat offspring, Am J Physiol Endocrinol Metab 316 (4) (2019) E622–E634.
[142] G. Desideri, R. Gentile, A. Antonosante, E. Benedetti, D. Grassi, L. Cristiano, et al., Uric acid amplifies Abeta amyloid effects involved in the cognitive dysfunction/dementia: evidences from an experimental model in vitro, J Cell Physiol 232 (5) (2017) 1069–1078.
[143] H.C. Williams, B.C. Farmer, M.A. Piron, A.E. Walsh, R.C. Bruntz, M.S. Gentry, et al., APOE alters glucose flux through central carbon pathways in astrocytes, Neurobiol Dis 136 (2020), 104742.
[144] L.C. Walker, M. Jucker, The exceptional vulnerability of humans to Alzheimer's disease, Trends Mol Med 23 (6) (2017) 534–545.
[145] T. Arendt, J. Stieler, A.M. Strijkstra, R.A. Hut, J. Rüdiger, E.A. Van der Zee, et al., Reversible paired helical filament-like phosphorylation of tau is an adaptive process associated with neuronal plasticity in hibernating animals, J Neurosci 23 (18) (2003) 6972–6981.
[146] A. Taguchi, L.M. Wartschow, M.F. White, Brain IRS2 signaling coordinates life span and nutrient homeostasis, Science 317 (5836) (2007) 369–372.
[147] A.A. Khan, T.J. Quinn, J. Hewitt, Y. Fan, J. Dawson, Serum uric acid level and association with cognitive impairment and dementia: systematic review and meta-analysis, Age (Dordr). 38 (1) (2016) 16.
[148] S.M. Lee, A.L. Lee, T.J. Winters, E. Tam, M. Jaleel, P. Stenvinkel, et al., Low serum uric acid level is a risk factor for death in incident hemodialysis patients, Am J Nephrol 29 (2) (2009) 79–85.
[149] H. White, C. Pieper, K. Schmader, The association of weight change in Alzheimer's disease with severity of disease and mortality: a longitudinal analysis, J Am Geriatr Soc 46 (10) (1998) 1223–1227.
[150] D.K. Johnson, C.H. Wilkins, J.C. Morris, Accelerated weight loss may precede diagnosis in Alzheimer disease, Arch Neurol 63 (9) (2006) 1312–1317.
[151] M.A. Beydoun, H.A. Beydoun, Y. Wang, Obesity and central obesity as risk factors for incident dementia and its subtypes: a systematic review and meta-analysis, Obes Rev 9 (3) (2008) 204–218.
[152] J.K. Maesaka, G. Wolf-Klein, J.M. Piccione, C.M. Ma, Hypouricemia, abnormal renal tubular urate transport, and plasma natriuretic factor(s) in patients with Alzheimer's disease, J Am Geriatr Soc 41 (5) (1993) 501–506.
[153] S.K. Lee, M.A. Lanaspa, L.G. Sánchez-Lozada, R.J. Johnson, Hyponatremia with persistent elevated urinary fractional uric acid excretion: evidence for proximal tubular injury? Kidney Blood Press Res 41 (5) (2016) 535–544.
[154] R.C. Morris Jr., An experimental renal acidification defect in patients with hereditary fructose intolerance. II. Its distinction from classic renal tubular acidosis; its resemblance to the renal acidification defect associated with the Fanconi syndrome of children with cystinosis, J Clin Invest 47 (7) (1968) 1648–1663.
[155] D.J. Schretlen, A.B. Inscore, H.A. Jinnah, V. Rao, B. Gordon, G.D. Pearlson, Serum uric acid and cognitive function in community-dwelling older adults, Neuropsychology 21 (1) (2007) 136–140.
[156] B.F. Verhaaren, M.W. Vernooij, A. Dehghan, H.A. Vrooman, R. de Boer, A. Hofman, et al., The relation of uric acid to brain atrophy and cognition: the Rotterdam Scan Study, Neuroepidemiology 41 (1) (2013) 29–34.
[157] J.Y. Hong, T.Y. Lan, G.J. Tang, C.H. Tang, T.J. Chen, H.Y. Lin, Gout and the risk of dementia: a nationwide population-based cohort study, Arthritis Res Ther 17 (2015) 139.
[158] B. Engel, W. Gomm, K. Broich, W. Maier, K. Weckbecker, B. Haenisch, Hyperuricemia and dementia - a case-control study, BMC Neurol 18 (1) (2018) 131.
[159] T.J. Chuang, Y.H. Wang, J.C. Wei, C.J. Yeh, Association between use of anti-gout preparations and dementia: nested case-control nationwide population-based cohort study, Front Med (Lausanne) 7 (2020), 607808.
[160] K.H. Min, S.O. Kang, S.J. Oh, J.M. Han, K.E. Lee, Association between gout and dementia in the elderly: a nationwide population-based cohort study, Am J Geriatr Psychiatry 29 (12) (2021) 1177–1185.
[161] J.A. Singh, J.D. Cleveland, Gout and dementia in the elderly: a cohort study of Medicare claims, BMC Geriatr 18 (1) (2018) 281.
[162] C. Gersch, S.P. Palii, W. Imaram, K.M. Kim, S.A. Karumanchi, A. Angerhofer, et al., Reactions of peroxynitrite with uric acid: formation of reactive intermediates, alkylated products and triuret, and in vivo production of triuret under conditions of oxidative stress, Nucleosides Nucleotides Nucleic Acids 28 (2) (2009) 118–149.
[163] Parkinson Study Group SURE-PD3 Investigators, M.A. Schwarzschild, A. Ascherio, C. Casaceli, G.C. Curhan, R. Fitzgerald, et al., Effect of urate-elevating inosine on early Parkinson disease progression: the SURE-PD3 randomized clinical trial, JAMA 326 (10) (2021) 926–939.
[164] R.E. Gonsette, C. Sindic, M.B. D'Hooghe, P.P. De Deyn, R. Medaer, A. Michotte, et al., Boosting endogenous neuroprotection in multiple sclerosis: the Association of Inosine and Interferon beta in relapsing- remitting Multiple Sclerosis (ASIIMS) trial, Mult Scler 16 (4) (2010) 455–462.
[165] T.A. Johnson, H.A. Jinnah, N. Kamatani, Shortage of cellular ATP as a cause of diseases and strategies to enhance ATP, Front Pharmacol 10 (2019) 98.
[166] H. Watanabe, T. Hattori, A. Kume, K. Misu, T. Ito, Y. Koike, et al., Improved Parkinsons disease motor score in a single-arm open-label trial of febuxostat and inosine, Medicine (Baltimore) 99 (35) (2020), e21576.
[167] Early-onset dementia and Alzheimer's rates grow for younger American adults, Blue Cross Blue Shield [Internet]. 2020 [cited 2022 Dec 14]. Available from: https://www.bcbs.com/the-health-of-america/reports/early-onset-dementia-alzheimers-disease-affecting-younger-american-adults.
[168] Alzheimer's disease facts and figures, Alzheimers Dement 17 (3) (2021) 327–406, 2021.
[169] G. Cipriani, C. Lucetti, A. Nuti, S. Danti, Wandering and dementia, Psychogeriatrics 14 (2) (2014) 135–142.