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Could Alzheimer's Disease Be a Maladaptation of an Evolutionary Survival Pathway Mediated by Intracerebral Fructose and Uric acid Metabolism?

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Abbreviations: AD, Alzheimer's disease; AMP, adenosine monophosphate; AMPD2, AMP deaminase-2; AMPK, AMP-activated protein kinase; ApoE4, Apolipoprotein E4; ATP, adenosine triphosphate; CMRglc; cerebral metabolic rate for glucose;FDG-PET, [^{18}F]-fluoro-2-deoxy-D-glucose positron emission tomography scan; HFCS, high fructose corn syrup; KHK, ketohexokinase; MCI, Mild Cognitive Impairment; NADPH oxidase, nicotinamide adenine dinucleotide phosphate oxidase OXPHOS, mitochondrial oxidative phosphorylation.

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 the resting human amounts to 20 % of 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 by multiple ways, including by 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. While 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 if there is potential benefit in the prevention, management or treatment of this disease. (Word count 260)

Key Words: Alzheimer's Disease, Fructose, Metabolic Syndrome, Insulin Resistance, Energy Metabolism

Alzheimer's disease (AD) is currently the third leading cause of death and is characterized by cognitive decline and cerebral atrophy that is associated with beta amyloid plaques and tau protein aggregation (neurofibrillary tangles) in neurons. Treatments to reduce beta 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 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 Alzheimer's, and 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 assure enough food, water and oxygen for survival. While acute survival responses to starvation (7) are well known, nature has also developed a way to protect animals *before* the crisis actually occurs (8). We have shown this "survival response" is mediated by the metabolism of fructose that is either ingested or produced in the body. While biological effects of fructose metabolism, and its byproduct, intracellular uric acid, appear critical for survival of many animals in nature, including our ancestors, in modern society it appears to be over-engaged, 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, as the brain has high energy requirements, accounting for 20 percent of the daily adenosine triphosphate (ATP) used by the body despite constituting only 2 percent of the body mass. As much of the protection of the survival pathway is mediated by a reduction in systemic ATP production and usage (8), one might wonder if 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 to AD.

A Survival Pathway Triggered by Fructose

Many foods are known to have physiological effects in addition to their caloric content. Sugary beverages, for example, are particularly associated with the development of obesity and diabetes (10)

and this has been proposed to be due to its fructose content (11, 12). Indeed, excessive fructose ingestion can induce all components of the metabolic syndrome (13). This has been shown to be due not to its caloric metabolism but rather is mediated by on 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).

Subsequent research has found evidence that excessive intake and metabolism of fructose is used by animals in nature to activate a survival response that prepares animals 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 by stimulating foraging (20-22). The demand for oxygen is reduced by slowing mitochondrial respiration with a shift towards glycolysis (23, 24). The storage of fat and glycogen in the liver is encouraged by both stimulating their production and inhibiting fatty acid oxidation, lipolysis, and glycogenolysis (15, 25, 26). Glucose metabolism in muscle is reduced by decreasing glucose uptake (via insulin resistance) and by inhibiting insulin secretion from the pancreas; this both 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 the metabolic syndrome, including the development of obesity, by engaging the vasopressin V1b receptor (16). The accumulation of fat by vasopressin is another mechanism by which vasopressin conserves water, as 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 two major simple sugars, glucose and fructose, have opposing biologic effects. Glucose is the primary fuel for immediate energy demands, while fructose provides for future energy demands (**Figure 1**) (8). In effect, fructose causes a shift in cell metabolism such that the energy generated from the calories ingested are preferentially stored as fat and glycogen as opposed to immediate oxidation for ATP generation, a maneuver that preserves energy balance.

The biochemical mechanism is mediated by the rapid depletion of ATP from the initial phosphorylation of fructose by the enzyme fructokinase (also known as ketoxhexokinase or KHK) (**Figure**

1). The ATP levels are not immediately replenished as fructose 1-phosphate pools due to a slower flux through aldolase B. The cell responds to lower ATP levels by lowering adenosine monophosphate (AMP) levels to maintain the energy ratio. AMP degradation is mediated by AMP deaminase-2 (AMPD2) that produces ammonia and eventually uric acid (30). Uric acid translocates NADPH 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 (AMPK) (25). The net effect is to switch to a low power mode in which production and utilization of ATP are slowed down while intracellular ATP levels remain low (32).

The decline in intracellular ATP functions as an alarm, initiating processes that induce all features of the metabolic syndrome (8) The three primary drivers appear to be fructose, its byproduct uric acid, and vasopressin, the latter primarily from its actions on 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 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 way to activate this survival response, such as what occurs in the autumn when bears prepare for hibernation. However, fructose is also produced in the body by 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 (such as from hypoxia or ischemia) (32, 37), when water supplies are low (such as from 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 of the 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, as mice that have fructokinase knocked out in the liver are protected from fructose-induced weight gain and metabolic syndrome (17). While intake of fructose is a major way 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 as well as other organs (36, 41) , thereby activating the survival switch and inducing the metabolic syndrome (14, 39, 40). Indeed, the three tastes (sweet, salt and umami) that identify pleasurable foods likely developed to stimulate intake of foods that could activate the survival switch, while tastes for bitter and sour help identify foods that might contain toxins (42).

Humans have put this biological switch into overdrive due to two historic events. First, we are more sensitive to the effects of fructose because the enzyme uricase was lost in our primate ancestors due to 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 mid-Miocene (9).

The second more proximate factor has been the dramatic rise in intake of added sugars that contain fructose and glucose, such as from table sugar (sucrose) and high fructose corn syrup (HFCS) (13). Western diet contains a high content of fructose (primarily from sucrose and HFCS), as well as foods that stimulate fructose production (high glycemic carbohydrates, alcohol and salty foods) or 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) as well as genetic and environmental factors. Interestingly, whole fruits tend to not activate this pathway due to relatively low fructose content in individual fruit, 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 about 20 percent of the overall energy at rest, of which most is used by the neurons (70 to 80 percent) (47). The high energy needs of the neurons is accomplished by mitochondrial oxidative phosphorylation (OXPHOS) of glucose which requires sufficient oxygen to be present. The neurons themselves have poor back-up capacity as neurons generate very little ATP from glycolysis due to an impaired ability to upregulate phosphofructokinase (48). Beta oxidation of fatty acids

is also limited, which may relate to the higher oxygen requirements compared to glucose oxidation that would enhance the risk for local hypoxia (49).

The favored fuel for neurons is glucose, and there is even experimental evidence 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, and then they provide the lactate they generate to the neurons where it 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 which can provide glucose to the neuron 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 that can assist mitochondrial respiration, although this fallback strategy provides only 60 percent of the energy needs of 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 HIF1α 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 death of the astrocyte. Experimental studies suggest that astrocytes can survive when incubated with Aβ amyloid by increasing glycolytic activity, but if glycolysis is blocked, then astrocytes develop reactive gliosis and die by apoptosis while Aβ amyloid further accumulates (55).

Fructose and Alzheimer's Disease

The fructose survival pathway helps preserve critical brain functioning during the period of starvation by inducing systemic insulin resistance that preferentially provide glucose to the brain (**Table 3**). The pathway also stimulates foraging that costs energy, but this is made up by reducing resting energy metabolism. But given that the significant energy needs of the brain, how does this pathway affect cerebral energy metabolism?

Interestingly, foraging requires the inhibition of metabolism in various areas of the brain. Foraging requires rapid assessment (limiting deliberation), impulsivity (limiting self-control and reasoning), exploratory behavior and risk taking (limiting recent memory). Foraging does require 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, foraging is enhanced by inhibiting activity in cortical regions

involved in control and reasoning, by inhibition of the posterior cingulate cortex involved in disengagement from foraging (59) (60), and by blocking attention to time (entorhinal cortex). 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 regional reduction in brain energy metabolism, which would also conserve energy in settings where food availability is low (**Table 2**).

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, for 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 200 mg/dl, fructose levels increase in the brain, beginning around 30 minutes and peaking at 2 hours (65). However, the studies that evaluated the differences between fructose and glucose on cerebral metabolism using bold MRI were performed early (around 15 minutes) thus making it more likely to reflect true differences between fructose and glucose. Here, the striking finding was that fructose reduced blood flow to the posterior cingulate cortex, the hippocampus, the thalamus, and the occipital cortex (61), although 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 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 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, studies of AD show that the anterior cingulate and occipital cortex are typically spared (66). This corresponds very well to the regions affected by fructose and are in opposition to that observed with glucose.

Our hypothesis is that the fructose-dependent reduction in cerebral metabolism in these regions was initially reversible and meant to be beneficial. But chronic and persistent reduction 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 local fructose generation and metabolism may be the critical factor for how fructose induces AD since normally only 1 to2 percent 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 brain uric acid levels. 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 AMP deaminase 2 (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 of the KHK appears to be the A isoform(74). While this isoform does not typically induce ATP depletion in the liver, the relatively lower affinity for fructose-1-phosphate by the aldolase isozymes present in the brain (A &C) (75) make 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 Alzheimer's Disease are Associated with Fructose Metabolism

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

Aging is also associated with AD. Since diets high in carbohydrates and salt characterize much of the population, chronic endogenous fructose production could potentially explain this association. Consistent with this hypothesis, chronic intake of a diet containing 50 percent 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 western diet, which typically contains 50 percent carbohydrates, might also generate enough endogenous fructose to increase the risk for AD . Other risk factors for AD includes obesity, metabolic syndrome, insulin resistance, and diabetes (87-94), which are all conditions linked with intake of foods that either contain fructose or stimulate fructose production. Traumatic brain injury is a risk factor for AD and is expected to be increased local fructose production due to the local ischemia. Indeed, 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 AD Patients

There is also evidence that fructose production and metabolism is increased in the brains of AD patients, 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 nine AD subjects and nine age-matched controls. Sorbitol and fructose levels (both components of the polyol pathway) were significantly elevated, averaging 3 to 5-fold more 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 while the patient had no pre-mortem evidence of dementia, she had preclinical AD as noted by low brain weight and Braak Stage II histopathologic changes (96).

Fructose metabolism produces large amounts of lactate (97) in addition to consuming ATP (30). This is associated with AMP accumulation that is metabolized by AMPD2 to generate ammonia, hypoxanthine and, eventually, uric acid (**Figure 1**). Of interest, 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 but this eventually falls as disease progresses (98, 99). Likewise, lactate levels are 4-fold higher in the brains of subjects with early AD (99).

A metabolomic study of cerebral spinal fluid (CSF) found high hypoxanthine and xanthine levels in subjects with mild cognitive impairment (MCI) compared to controls, and xanthine was also higher in subjects with AD(100). Uric acid levels were also 25% higher in MCI subjects compared to 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 appear 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 disease progresses may be explained by the progressive decrease in intracellular ATP production associated with progressive impairment in mitochondrial function. Since uric acid is generated largely from the degradation of ATP, there will be less uric acid made as ATP production and turnover decreases. Indeed, there is a decrease in brain ATP levels of about 7 percent in early AD that progressively worsens over time (103). This might constitute a negative feedback system in an otherwise positive feedback system. Indeed, we found that fructose induced less of a rise in uric acid in individuals with type 2 diabetes and obesity that 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 scan (FDG-PET) (99, 105-107). The primary sites involved are the hippocampus, enterorhinal cortex, and the parietal, temporal and posterior cingulate cortex (105, 108). This is associated with a 50 percent reduction in ATP production from glucose metabolism and overall a 20 percent reduction in brain ATP production (109).

One mechanism for the hypometabolism is decreased glucose uptake (108). This is mediated in part by a reduction in GLUT1 in astrocytes and GLUT3 in the neurons of the AD patients (110, 111). While much of the brain does not require insulin for the uptake of glucose (112, 113), certain regions in the brain, such as the hippocampus, the hypothalamus, the striatum, and the parietal and frontal regions of the cerebral cortex are largely influenced by insulin (107, 114). The main glucose transporter that is insulin-dependent is GLUT4, and it is expressed in neurons in the hippocampus, hypothalamus, sensorimotor cortex and cerebellum (110). In AD there is both a reduction in insulin and insulin receptor A (IR-A) associated with insulin resistance (110, 115, 116). Impairment in GLUT4 function occurs as a consequence and this has a role in impairing cognitive function, especially in the hypothalamus (50).

While decreased glucose uptake is one mechanism for reduced glucose metabolism, AD is also associated with a decrease in 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 as

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 that two studies have actually measured glucose levels in AD and both found local glucose levels to be high (96, 111). Furthermore, when FDG-PET scan was performed with cognitive stimulation in subjects with early AD, one could demonstrate increased CMRglc as well as 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 capacity to increase brain ATP levels in response to challenging tasks. Further, reducing glucose metabolism with high levels of glucose being present due 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 by glycolysis (118) show reduced glycolysis, with decreased lactate production (51) and progressive senescence (119). Neurons also reduce ATP production due to a decrease in OX-PHOS (51). This also occurs in aging (120, 121). Neurons may produce some energy by glycolysis (at least in aging), as lactate uptake from neighboring astrocytes may be impaired due to a reduction in lactate transporters (moncarboxylate transporter proteins) in the neurons (122).

Oxidative stress is also increased in AD, as noted by accumulation of malondialdehyde (123), and is associated with mitochondria 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 utilize glycolysis(47) , thereby contributing to local neuroinflammation (125). Interestingly, peripheral white cells in AD patients show reduced aconitase, which would reduce 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 3**). For example, both fructose (127-129) and fructose-containing sugars (130, 131) can induce an impairment of spatial memory. Rats administered fructose in drinking water for 8 weeks develop hippocampal atrophy with reduced glucose uptake, decreased expression of

phosphorylated IR-A and insulin receptor substrate-1 , mitochondrial dysfunction, oxidative stress, with stimulation of NFkB and inflammatory cytokines and a decrease in ATP compared to rats receiving regular water (131). Giving fructose in the drinking water (10%) for a longer time (16 to18 weeks) model of AD results in obesity, decreases spatial memory, increased locomotor activity, cerebral insulin resistance (with low P13Kactivity and Akt levels), increased GSK3β expression, lower acetylcholine content, and the development of tau protein containing neurofilaments and Aβ amyloid plaques in the hippocampus when compared to rats given regular water (132-134). Administration of high doses of fructose to rats is also associated with greater mortality following stroke possibly due to a loss of astrocytes with greater neuroinflammation with hyperphosphorylation of tau protein (135) as well as hippocampal gliosis (136). Fructose administration is also associated with more beta 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 to lead to toxicity in culture (139) and likewise directly injecting fructose into the hypothalamus also 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 and reduced glycogen stores as well as decreased mitochondrial OX-PHOS and mitochondrial biogenesis (141).

As mentioned, fructose may induce its 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 done by stereotactic infusion of uric acid (68) and is associated with hippocampal gliosis by magnetic resonance imaging, 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. The Apolipoprotein E4 polymorphism (ApoE4) is a major risk factor for AD, raising the question of how it relates to the fructose hypothesis. Of interest, ApoE4 carriers showed reduced cerebral glucose metabolism by positron emission testing and also show reduced uptake

of glucose into astrocytes (143). ApoE4-derived astrocytes also show enhanced glycolysis despite less mitochondrial OX-PHOS and worse mitochondrial dysfunction compared to ApoE2 or ApoE3 astrocytes (143). The relative similarities in fructose effects on the brain with that observed with the ApoE4 polymorphism suggest parallel pathogenic mechanisms.

Species-specificity of AD. AD is relatively specific to humans, for while some primates show evidence for beta 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 in the brain during hibernation and this is reversible following 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 Receptor Knock-out Mice. Our hypothesis suggests that fructose acts to block brain glucose metabolism to aid survival by reducing total energy needs, stimulate effective foraging, and increasing weight, but if severe and prolonged would lead to brain atrophy and possible dementia. It is thus of interest that blocking insulin signaling in the brain can extend the life span of *Drosophila* and *C. elegans*. Selectively knocking out insulin receptor substrate-2 (Irs2) in the brain of mice, for example, extends life-span coupled with the development of obesity and insulin resistance (146). However, the knockout mice have reduced brain size (30%). In contrast, heterozygous mice lacking Irs2 live longer than normal mice but still develop metabolic complications although they do not develop the reduction in brain size (146).

Challenges and Limitations

If Uric Acid is Important in Driving Alzheimer's Disease, Why is it Low in AD Patients?

Numerous studies have reported that AD subjects have low serum uric acid levels suggesting this might be important to the pathogenesis (147). However, while 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) that may account for the lower serum uric acid levels on presentation of AD. This may also explain why obesity predicts AD in mid-life, but actually protects from AD late in life (151).

Some individuals with AD also lose excessive amounts of uric acid in their urine due to 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 percent) (152). Interestingly, this finding may reflect activation of the polyol-fructose pathway in the kidney (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 risk (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 to subjects with untreated gout (158-160). In one study, the use of febuxostat (a xanthine oxidase inhibitor) reduced the risk for dementia by 80 percent (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 of these diseases (163, 164). Furthermore, the use of inosine is problematic, for while it increases serum uric acid, inosine can enter the purine salvage pathway to stimulate ATP production (165). Some investigators have administered allopurinol with inosine to block uric acid formation as this encourages more of the inosine 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, shouldn't it be Increasing In Parallel with Obesity and Diabetes?

Given that the risk for AD is increased by western diets, as well as by obesity and diabetes, one might predict that that the sporadic (nonfamilial) form of AD should have increased dramatically during the twentieth century. Unfortunately, there are not good data to know whether this is actually the case. While AD was reported infrequently in the early twentieth 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 Alzheimer's Disease increased dramatically between 2013 and 2017 (167). Today Alzheimer's disease affects 10 percent of subjects in the USA over age 65 (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. While the pathway was meant to be beneficial, the mutation in uricase amplified the switch, while the introduction of western diet provided ample fuel to put it in high gear, with the result that the attempt to conserve energy has led to a severe reduction in the energy required to maintain the needs of the neurons. Indeed, the wandering response, which is so common in AD (169), may signify a persistent foraging response despite massive neuronal loss.

While available data supports our hypothesis(es), further studies are needed, particularly with a focus on individuals at risk, on individuals with MCI, and on subjects with early AD. Treatment trials that interrupt the pathway, including by 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 on the role of fructose and diet in this condition.

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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	From 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, inhibition of lipolysis	Fat accumulation in adipose, 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 Gut and Salt Reabsorption by Kidney	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 Setting of Poor Nutrient Intake	Impair Renal Autoregulation Activation of the Renal Angiotensin System	Elevation of glomerular hydrostatic pressure to assist filtration

KEY: ATP, adenosine triphosphate; BP, blood pressure.

Table 2 Beneficial Effects of Fructose Survival Switch on Brain Function

	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 ability to find food
Reduce Energy Metabolism in Brain	Reduce Glucose Metabolism in Special Regions of the Brain	Help Conserve overall Energy Needs

Key: V1b, vasopressin 1b receptor

Table 3 Parallels Between Early Alzheimer's Disease and Intracerebral Effects of Fructose Metabolism

	Early Alzheimer's Disease	**Fructose Metabolism**
Factors Associated with Increased Risk	Diet (sugar, high glycemic, high salt) Phenotype (diabetes, obesity, metabolic syndrome)	Diet (sugar, high glycemic, high salt) Phenotype (diabetes, obesity, metabolic syndrome)
Factors Associated with Decreased Risk	Diet (vegetables, dairy)	Diet (vegetables, dairy)
Preferential Regions Affected	Hippocampus, Entorhinal Cortex, Posterior cingulate cortex, Middle temporal gyrus, Sensomotor cortex	Hippocampus, 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 Reduce ATP Level	Decreased Glycolysis (possible early stimulation) Reduced Mitochondrial Function Reduce ATP Level
Fructose Metabolic Pathways	Increased AMPD2, increased fructose and sorbitol levels, uric acid elevated in early disease	Increased AMPD2, increased fructose and sorbitol levels, increased intracellular uric acid early

Key:

Figure Legends

Figure 1 The Fructose Survival Pathway. Fructose is metabolized by fructokinase to generate fructose-1-phosphate and then is metabolized like any caloric sugar. However, the initial phosphorylation is associated with rapid ATP consumption with a fall in intracellular phosphate that uniquely activates AMP deaminase-2, which subsequently removes the AMP to generate uric acid. In turn, uric acid induces NADPH oxidase activation in the mitochondria, leading to oxidative stress that blocks the citric acid cycle (via inhibition of aconitase) and also beta fatty acid oxidation. As mitochondrial function slows, glycolysis takes over, while uric acid also inhibits AMP activated protein kinase that reduces the ability to recover ATP. The effect is a fall in ATP in the cell, activating a survival switch that includes hunger, thirst, foraging, fat accumulation, and insulin resistance. **Key**: AMP, adenosine monophosphate; ATP, adenosine triphosphate. Yellow circles show steps that assist in lowering ATP levels in the cell.

Figure 2 How Foods and Stress Engage the Fructose Survival Pathway. Fructose can come directly from the diet (such as from added sugars containing sucrose or high fructose corn syrup) or from high glycemic carbohydrates. The latter generates glucose which can be converted via the polyol pathway to fructose due to activation of the rate-limiting enzyme, aldose reductase. Aldose reductase can be activated by salty foods, high glycemic foods or alcohol that all increase serum osmolality. In turn, the fructose then activates the switch. Interestingly, umami foods that are rich in glutamate and or purines (such as AMP or IMP) can also enter the switch distal to the fructose step. **Key:** AMP, adenosine monophosphate; ATP, adenosine triphosphate; HFCS, high fructose corn syrup; KHK, fructokinase; IMP, inosine monophosphate.

Figure 3 Evidence for Activation of the Polyol Pathway in the Brains of Alzheimer's Disease. The endogenous production of fructose can only occur from the conversion of glucose to sorbitol and then to fructose by the polyol pathway. One study found approximately four to five-fold higher levels of both sorbitol (Figure A) and fructose (Figure B) in the post-mortem brains of nine patients with Alzheimer's disease compared to a similar number of controls (96). Key: HIP, hippocampus; ENT, entorhinal cortex; CING, cingulate gyrus; SEN, sensory cortex; MOT, motor cortex; TEM, midle temporal gyrus; CER, cerebellum.

Figure 1

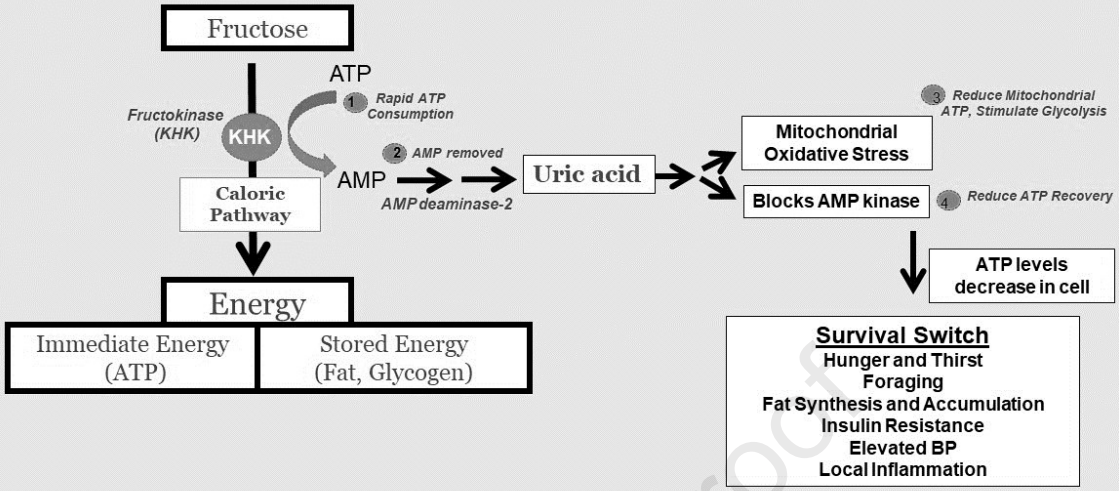

Figure 2