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High carbohydrate diets and Alzheimer's disease

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Summary Alzheimer's disease (AD) is a common, progressive, neurodegenerative disease that primarily afflicts the elderly. A well-defined risk factor for late onset AD is possession of one or more alleles of the epsilon-4 variant (E4) of the apolipoprotein E gene. Meta-analysis of allele frequencies has found that E4 is rare in populations with long historical exposure to agriculture, suggesting that consumption of a high carbohydrate (HC) diet may have selected against E4 carriers. The apoE4 protein alters lipid metabolism in a manner similar to a HC diet, suggesting a common mechanism for the etiology of AD. Evolutionarily discordant HC diets are proposed to be the primary cause of AD by two general mechanisms. (1) Disturbances in lipid metabolism within the central nervous system inhibits the function of membrane proteins such as glucose transporters and the amyloid precursor protein. (2) Prolonged excessive insulin/IGF signaling accelerates cellular damage in cerebral neurons. These two factors ultimately lead to the clinical and pathological course of AD. This hypothesis also suggests several preventative and treatment strategies. A change in diet emphasizing decreasing dietary carbohydrates and increasing essential fatty acids (EFA) may effectively prevent AD. Interventions that restore lipid homeostasis may treat the disease, including drugs that increase fatty acid metabolism, EFA repletion therapy, and ketone body treatment.

Introduction

The clinical course of Alzheimer's disease (AD) typically begins in the seventh or eighth decade and is characterized by disturbances in memory, language, and spatial skills, all of which worsen as the disease progresses. Upon autopsy, extensive neuritic plaques and neurofibrillar tangles are found in the brain, as well as gross structural changes, such as loss of neurons in the hippocampus, nucleus basalis and other areas (for overview see [1]). There are no effective treatments and the disease invariably progresses until death.

The cause of AD has been the subject of intense debate. The current favored model is the amyloid cascade hypothesis, which proposes that peptides generated from the amyloid precursor protein (APP) are the causative factor and reducing the generation or accumulation of these peptides will treat the disease (for overview see [2]). However, others have proposed that diet may be the primary cause. In 1997, William Grant correlated the amounts and types of foods consumed in different countries with the prevalence of AD and found a positive association between both total calories and total fat and the incidence of the disease [3]. Kalmijn et al. [4] also noted a correlation between fat intake and dementia in a study of 5386 participants in Rotterdam. These important studies pointed toward a strong environmental component

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to AD and suggested that dietary modification might prevent the disease. However, follow-up studies have failed to confirm this link [5]. This highlights the difficulties in identifying environmental risk factors in large diverse populations with many variables, some of which may be omitted or hidden by cultural bias. For example, assumptions on what is considered normal intake of fat, protein and carbohydrate depends greatly on where and when you look.

The analysis presented here suggests that AD results not from high-fat diets, but rather from high-carbohydrate diets (HC). This view is supported by the genetic association of AD with the epsilon 4 allele of the apolipoprotein E gene (E4), the role of lipids in APP processing, and the role of insulin/IGF signaling in aging. A molecular model is presented as well as preventative and treatment strategies. Furthermore, this analysis supports the view that AD is similar to type II diabetes, obesity, and coronary heart disease, in that it results from the conflict between our Paleolithic genetic makeup and our current Neolithic diet.

Agriculture was abomination

The conflict between our genetic makeup and our diet is similar to the concept of the "thrifty genotype" proposed by James Neel in a landmark work to explain prevalence of type II diabetes in modern society. "thrifty" was used to mean "... being exceptionally efficient in the intake and/or utilization of food." [6]. He proposed that pre-agricultural hunter-gatherers went through cycles of feast or famine which led to the selection of a metabolism that would readily store fat, and obesity and type II diabetes result when this genetic makeup is confronted with the modern abundance of food. An alternative to this model is that the abundance of food did not change, rather the type of food did.

In a translation of the classic Indian text The Ramayana, the adoption of agriculture is depicted not as a revolution, but as an abomination. "In the Golden Age, agriculture was abomination... For the existence of sin in the form of cultivation, the lifespan of people became shortened." [7]. Such a view is consistent with the hypothesis that agriculture (The Neolithic Revolution) arose out of necessity rather than cleverness. Several authors have argued that present day hunter-gatherers are well aware of the concepts of agriculture but do not practice it because it requires too much labor [8]. Instead they propose that humans adopted agriculture only when wild game became scarce and they had no other choice (for overview see [9]). In fact, Paleolithic hunter-gatherers are likely to have caused the scarcity of wild game. Recent evidence suggests that they were extremely productive hunters, especially of big game, and over hunting was a major factor in the extinction of mega-fauna in North America [10] and Australia [11].

To understand the dietary shift brought about by the Neolithic Revolution it is necessary to reconstruct the Paleolithic diet. In an earlier work, Eaton and Konner estimated a plant:animal ratio of 65:35 and a fat:protein:carbohydrate ratio of 21:34:45 [12]. In an updated analysis, Cordain et al. [13] estimate a much higher fat intake. They conclude that most hunter-gatherers (73%) derived greater than 50% of their diet from animal sources, suggesting a reversal of the plant:animal ratio from 65:35 to 35:65. They also propose a macronutrient range of approximately 40:30:30. Both studies conclude that protein was a significant part of the diet, while fat and carbohydrate content varied by location. Those living at higher latitudes tended to eat more fat, while those in more tropical latitudes tended to eat more plant matter. Yet, most hunter-gatherers ate animal matter when available [13]. Such a large protein intake is consistent with the tall stature of Upper Paleolithic humans [14], and of pre-agricultural Native Americans [15]. Male Late Paleolithic hunter-gatherers are estimated to have been an average of 177 cm tall, similar to average male heights in the developed world today [16].

It should be noted that the carbohydrates consumed during the Paleolithic period were very different from the high-glycemic carbohydrates found in modern diets and from the breads and grains consumed by Neolithic farmers. Consumption of plant matter does not necessarily result in a large intake of carbohydrates. For some plant matter, as much as 30—100% of the energy is released in the form of short chain fatty acids produced by hind gut fermentation of fiber [17]. A good analogy might be modern primate diets. In an analysis of gorilla diet, which consists almost exclusively of fruits and vegetables, a macronutrient profile of fat:protein:carbohydrate was calculated at approximately 3:24:16, with the remaining 57% of the energy in the form of short chain fatty acids derived from fiber [18]. Therefore, Paleolithic diets, rich in animal products and fruits and vegetables, may have been a low-carbohydrate diet (~20% of energy).

The diets of Neolithic farmers were of much poorer quality than Late Paleolithic hunter-gatherers and this has been implicated in the overall decline in health during the Neolithic period (for overview see [19]). For example, average height of a male Late Neolithic farmer was 161 cm,

a full 16 cm shorter than a male Late Paleolithic hunter-gatherer [16]. Stature is known to be strongly influenced by diet, especially protein intake, and is frequently used as a measure of nutritional status [16]. It is likely that the Neolithic diet was very high in carbohydrates and low in protein, consistent with depletion of wild game as a major motivator for the development of agriculture. This dependence on grain-based agriculture resulted in a long period of reduced stature in humans. Only in modern times has average height returned to Late Paleolithic standards [12].

ApoE4 and agriculture

While the shift to HC diets during the Neolithic Revolution resulted in a general decline in health, it proved particularly disastrous to carriers of the epsilon 4 allele of apolipoprotein E. Currently, the only well defined genetic risk factor for late onset Alzheimer's disease is allelic variation in the apolipoprotein E gene (apoE). The main function of the apoE protein is lipid transport, but as such, it has an impact on a variety of cellular processes. There are three common allelic variants of apoE: epsilon 2 (E2), 3 (E3) and 4 (E4) (for review see [20]). Possession of the E4 variant increases the risk of developing AD and behaves in a dominant dose dependent manner [21]. E4 is also a risk factor for coronary heart disease [22] and poor recovery from head trauma [23]. Why such a "deleterious" allele would be selected against in some populations but not in others may provide an important clue to the etiology of AD.

The alleles E2, E3 and E4 are not evenly distributed in all populations. In a meta-analysis of published apoE allele frequencies, Corbo and Scacchi noted that E4 is under-represented in populations with long historical exposure to agriculture, and they proposed that E4 may be a thrifty allele [24]. Populations with the lowest frequencies of E4 include long time agriculturalists, such as Greeks (0.068) and Turks (0.079), while populations with the highest frequencies include long time hunter-gatherers, such as African Pygmies (0.407), Papuans (0.368), and Inuits (0.214) [24]. This has been supported by a study of Arab populations living in northern Israel who had the lowest E4 frequency ever recorded (0.04) [25]. One interpretation of this distribution is genetic drift due to migration of populations out of the Middle East (see Fig. 1). The migration of Neolithic farmers

Figure 1 Distribution of apolipoprotein E epsilon 4 allele (E4), adapted from [24,25]. Frequency of E4 is low (light regions) in historically agriculture-based societies in the Middle East and in Central America (inset). Arrows indicate migration of Neolithic farmers from the Middle East along the Mediterranean Sea.

along the Mediterranean Sea is based on historical records and confirmed by analysis of the Y chromosome [26]. However, such a migration does not explain the low frequency of E4 found in North American Mayan populations (0.089) [24]. The Mayan civilization arose in what is present day Mexico and Guatemala, far from the Middle East and in a very different ecological environment. Yet, the Mayans were similar to Middle Eastern farmers in that they also developed an extensive agricultural society based primarily on maize. Therefore, consumption of an HC diet, either derived from corn or wheat, may have selected against the E4 allele.

Why would E4 be deleterious to populations consuming a HC diet? Possession of an E4 allele is frequently associated with elevated plasma cholesterol and LDL-cholesterol levels and this association is normally attributed to consumption of a high-fat, high-cholesterol diet (for overview see [27]). One interpretation of such a view is that Neolithic farmers ate a diet much like a modern Western atherogenic diet, rich in animal fat and cholesterol, and that E4 was selected against by widespread prevalence of coronary heart disease. This seems unlikely. It is more likely that Neolithic farmers ate little animal matter, were protein starved, and are better characterized as "...ant-like armies of largely vegetarian workers." [9]. Instead it can be argued that HC diets and possession of an E4 allele both suppress lipid metabolism in a similar manner and, in combination, greatly increase the risk for coronary heart disease and AD.

HC diets, ApoE and lipid metabolism

The effect of HC diets on lipid metabolism is evident in the fate of triglyceride rich lipoproteins (TRL), such as chylomicrons and very low density lipoproteins (VLDL) (for overview see [28]). The rate of clearance of TRL and the type of cells that take up free fatty acids (FFA) depends mainly on the activity of lipoprotein lipases (LPL) and is strongly influenced by insulin signaling [29]. It is well recognized that HC diets elevate VLDL levels and can result in hypertriacylglycerolemia (for review see [30]). This may be due to decreased LPL activity and fatty acid use by muscle cells [29,31]. For example, Lithell et al. [32] studied 7 men fed either high carbohydrate (HC, greater than 70% of calories from carbohydrate) or high fat (HF, greater than 70% of calories from fat) diets for 3 days. Those consuming the HC diet had statistically increased insulin levels and decreased lipase activities relative to the HF diet. These experiments are consistent with the proposed fuel use hierarchy in humans, such that glucose is used preferentially over fat [33]. In particular, HC diets inhibit the use of fatty acids and increase the residence time of TRL (for review see [34]).

Much like a HC diet, the ApoE4 protein increases TRL residence time by inhibiting lipolysis. ApoE4 binds TRL much more readily than ApoE2 or ApoE3 and will displace ApoCII resulting in decreased LPL activity (see Fig. 2(***I***)), for review see [35]). For example, in a study of young men consuming a high fat meal (39% fat calories) TRL were elevated in both E3/E3 and E3/E4 individuals. After 6 h, TRL returned to post-absorptive values in the E3/E3 individuals, yet remained elevated 50—80% in E3/E4 individuals [36]. Such elevated TRL have been observed numerous times in E4 carriers. In a meta-analysis of different populations, E4 carriers had significantly higher plasma triglyceride levels than those with E3 [37]. This decreased LPL activity may also be the cause of the increased insulin sensitivity observed in E4 carriers [38] possibly due to lowering of serum FFA levels (see Fig. 2(***III***)) (for overview see [39]).

Since E4 and HC diets inhibit lipid metabolism in a similar manner this may explain the selection against E4 in long-time agricultural societies. Symptoms of AD do not typically begin until the seventh decade so it is unlikely that AD was the selective force, instead it may have been coronary heart disease (CHD). The very HC diet of Neolithic farmers would have raised serum glucose and insulin levels, induced lipogenesis and led to hypertriacylglycerolemia. This would be worsened by possession of an E4 allele. Elevated triglycerides increase the risk of CHD and this may have selected against E4 in Neolithic farmers. Importantly, this same mechanism is likely to be responsible for the high risk of CHD in modern populations, with or without an E4 allele.

It should be noted that E4 is not an inherently damaging allele, it is only deleterious in combination with a HC diet (which is deleterious on its own). Populations with little exposure to HC diets have higher E4 frequencies suggesting it is not selected against in these conditions [24]. Also, E4 may not be a risk factor for AD in all populations, such as in Nigeria [40,41]. Nigerians eat considerably less high-glycemic carbohydrates than at risk populations such as the US. For example, in 1999, Nigerians consumed 20 kg/year of sugar per capita, compared with 74 kg/year for a typical American (source Food and Agriculture Organization of the United Nations statistical database, FAOSTAT). This may explain the low incidence of AD in Nigeria [42] despite the relatively high frequency of E4.

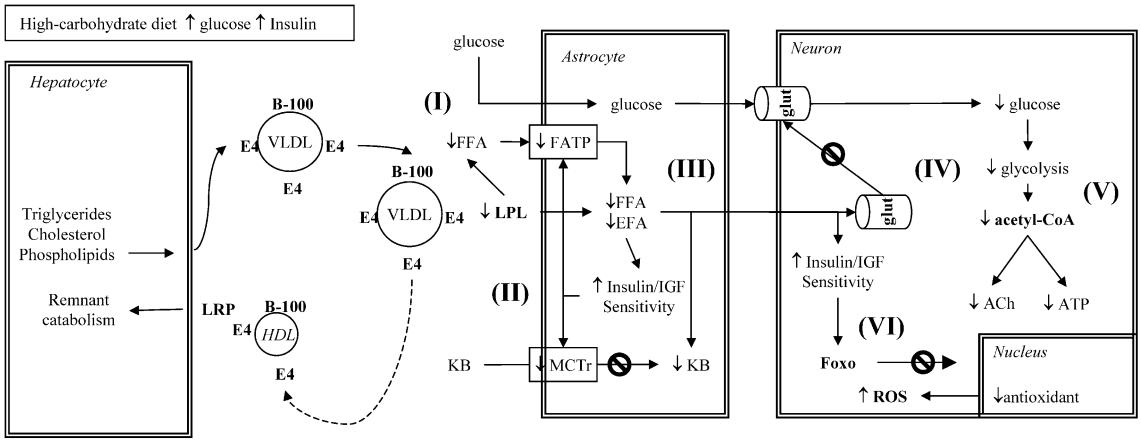

Figure 2 ApoE4 and a high carbohydrate diet inhibit lipid metabolism. Bold Roman numerals indicate key points in the model. (**I**) E4 preferentially binds triglyceride rich particles such as VLDL and chylomicrons reducing ApoCII binding. (**II**) Decreased LPL activity inhibits delivery of FFA to astrocytes. (**III**) Low FFA levels increase insulin sensitivity and further decrease LPL activity and ketone body transport. (**IV**) Inefficient delivery of EFA to cerebral neurons inhibits function of glucose transporters (GLUT). (**V**) Decreased metabolism lowers acetyl-CoA pools and levels of ATP and acetylcholine. (**VI**) Increased insulin signaling inhibits Foxo proteins from entering the nucleus and prevents activation of stress response genes, such as antioxidant proteins. Abbreviations: LRP — LDL receptor related protein, VLDL — very low density lipoprotein, HDL — high density lipoprotein, LPL — lipoprotein lipase, FFA — free fatty acid, MCTr — monocarboxylate transporter, E4 — ApoE4, FATP — fatty acid transport protein, KB — ketone bodies, ACh — acetylcholine, ROS — reactive oxygen species.

Prior to the development of agriculture, E2, E3 and E4 may have been neutral alleles that arose when our human ancestors began to eat more animal matter, and hence more fat, and this relaxed selection on apoE. The development of agriculture then imposed a new selection on apoE reducing E4 in Middle Eastern and Mayan populations.

Overview of the etiology of AD

HC diets are proposed as the primary cause of AD by two basic mechanisms (see Fig. 3 for overview). The first is disturbed lipid homeostasis within the CNS, especially decreased delivery of essential fatty acids (EFA) (see Fig. 3(***I***)). This compromises the integrity of cellular membranes, decreasing the function of membrane proteins such as glucose transporters and APP. The second is mild chronic elevated insulin/IGF signaling, which accelerates cellular damage (Fig. 3(***II***)). These two mechanisms contribute to two stages of the disease. Stage I begins when altered lipid metabolism inhibits the function of membrane proteins such as glucose transporters, resulting in decreased glucose utilization and lowered metabolism in susceptible regions of the brain. At this stage no clinical signs of dementia are evident, yet the disease has begun. Stage II begins when the inhibition of cellular function can no longer be compensated for, either due to excessive cellular damage, or age impaired loss of homeostatic mechanisms. In stage II, acetyl-CoA levels are lowered below critical levels, affecting the production of a variety of cellular components such as cholesterol and acetylcholine and clinical signs of dementia become evident. The disturbances in cholesterol metabolism result in large scale aberrant processing of APP, decreases in cellular trafficking, and generation of amyloid beta peptides (Aβ). As the disease progresses, the failure to transport neurotrophin receptors and the production of increasing amounts of Aβ ultimately results in large scale cell death and the characteristic pathology of AD.

Stage I — essential fatty acids and membrane function

Despite the importance of fatty acids in cerebral neurons little de novo fatty acid synthesis occurs in the adult brain (for overview see [43]). Most fatty acids are imported as phospholipids or unesterified FFA from the plasma through the use of fatty acid transport proteins (for review see [44]). One important class of fatty acids required by the CNS are EFA. For example, docosahexanoic acid (DHA) is found extensively in phospholipids of neuronal membranes (for overview see [45]). Inhibition of lipid metabolism by HC diets may mimic dietary

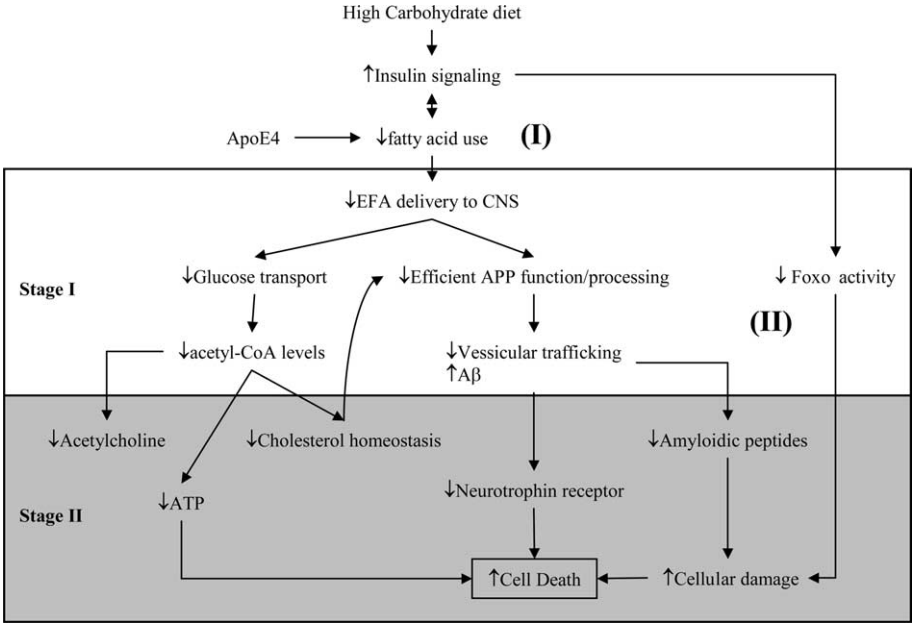

Figure 3 HC diet and Alzheimer's disease model overview. Light and shaded areas indicate stages of the disease. Bold Roman numerals highlight major mechanisms of disease progression. (I) HC diet and ApoE4 contribute to decreased lipid metabolism in central nervous system, altering the function of glucose transporters and amyloid precursor protein (APP). (II) Chronic excessive insulin/IGF signaling inhibits the functioning of Foxo proteins thereby increasing cellular damage.

deficiencies of EFA which are known to alter the composition of neuronal membranes, disturb the activity of membrane proteins [46], and lead to behavioral defects such as poor performance in learning tasks (for overview see [47]). This is consistent with the growing evidence that EFA play a role in AD. Low serum DHA levels have been implicated as a significant risk factor [48,49], and consumption of fish (a rich source of DHA and EPA) may prevent the disease [50]. Additionally, altered lipid metabolism may be responsible for the extensive membrane deterioration seen in AD [51,52].

In addition to metabolic changes induced by HC diets, the development of agriculture has directly changed the normal dietary balance of EFA. It has been estimated that Paleolithic hunter-gatherers ate roughly equal amounts of $n-6$ and $n-3$ fatty acids [12]. However, the modern Western food supply is much richer in $n-6$ fatty acids due to the use of grains both in the diet and as animal feed. This has greatly altered the ratio of dietary $n-6$ to $n-3$ fatty acids from roughly 1:1 for Paleolithic hunter-gatherers to $\sim$20:1 for a modern diet. The $n-6$ fatty acids compete for desaturases used by $n-3$ fatty acids to produce products such as DHA, essentially lowering their levels (for review see [53]).

One class of protein known to be effected by EFA levels are glucose transporters. For example, rats raised on a $n-3$ deficient diet for three months exhibit a 30–35% decrease in glucose uptake in the cortex, hippocampus and SCN compared to ad lib fed controls, due to inefficient function of glucose transporters [54]. Such decreases in cerebral glucose utilization are one of the earliest signs of AD and are evident in at risk populations well before clinical signs of dementia occur, particularly in E4 carriers [55]. Yet, at this early stage, poor cognitive performance may be masked by recruiting larger regions of the brain to accomplish mental tasks [56]. As the disease progresses, inhibition of glucose use worsens (for overview see [57]), and at some point declines to where recruitment can no longer compensate for energy loss (Fig. 3(*IV*)). This is the beginning of Stage II.

Stage II — metabolism, cholesterol and APP

Cerebral neurons are normally considered to derive acetyl-CoA almost exclusively from glucose. As glucose utilization worsens it will begin to deplete neuronal acetyl-CoA pools leading to decreased synthesis of acetylcholine (Fig. 3(*IV*)) and the well recognized cholinergic defects found in AD [58]. Another less obvious, but perhaps more important, consequence of lower acetyl-CoA levels is altera-

tions in cholesterol homeostasis (Fig. 4(*II*)). The human brain contains large amounts of unesterified cholesterol, roughly 25% of the total amount in the body. Unlike FFA, cholesterol is synthesized de novo within neuronal cells from condensation of acetyl-CoA and is part of a complex regulatory process of cholesterol homeostasis (for review see [59]). Disturbance in this process has been implicated in several neurological disorders, including AD. For example, allelic variation in the cyp46 gene (a cholesterol 24-hydroxylase) has been identified as a risk factor [60] and decreased cholesterol levels are found in affected regions of the brain [61].

One important protein that is sensitive to disturbances in cholesterol homeostasis is APP (Fig. 4(*III*)). Early onset AD is frequently associated with mutations in three genes; APP, presenilin 1 (PS1) and presenilin 2 (PS2). These mutations lead to aberrant processing of the APP protein and accumulation of the Aβ peptide (for review see [2]). Recent evidence has suggested that excess cholesterol leads to increased APP cleavage. Diet induced hypercholesterolemia increases the levels of Aβ and amyloid deposits in the CNS of transgenic mouse models of AD [62,63]. Addition of excess cholesterol to cells in culture increases Aβ production, while depleting cells of cholesterol decreases Aβ production (for overview see [64]). Also, treating animals with cholesterol lowering drugs (statins) decreases the levels of Aβ in the blood [65] and may decrease the risk of developing AD up to 70% [66]. Yet, most statin drugs do not cross the blood brain barrier and are predicted to have a weak, if any, effect on cerebral cholesterol production (for overview see [67]).

Alternatively, statins may protect against AD by improving cerebral lipid metabolism. In addition to inhibition of 3-hydroxy-3-methylglutaryl CoA reductase, statins have other physiologic effects, such as vasodilatory and anti-inflammatory. Importantly, statins also cause a reduction in circulating TRL by increasing the levels of lipoprotein lipase while also decreasing apolipoprotein C-III (an inhibitor of lipoprotein lipase) [68]. Therefore statins may directly counteract the effects of HC diets by increasing the activity of LPL.

Aβ may not be the only toxic result of aberrant APP processing. APP is proposed to function as a membrane cargo receptor for kinesin-I during axonal transport, delivering several cellular factors, including Bace (beta secretase), Ps1 (Presenilin 1), and the neurotrophin receptor TrkA [69—71]. Mutations in APP and the presenilins, as well as disturbed cholesterol homeostasis, may lead to premature cleavage of APP and inhibition of cel-

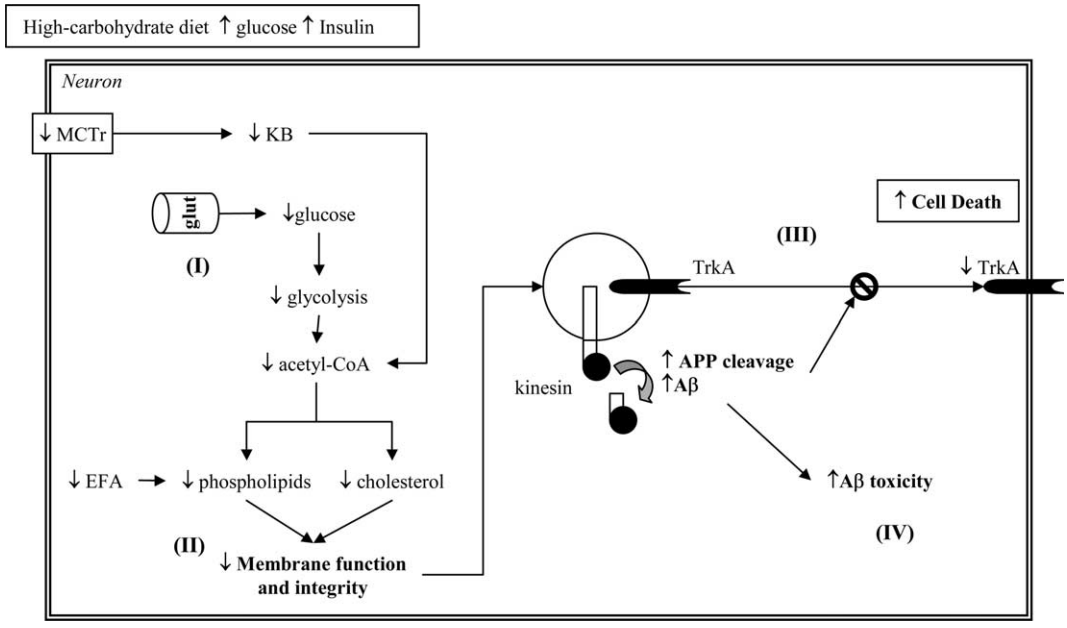

Figure 4 Lipid homeostasis and APP. Bold Roman numerals indicate key points in the model. (**I**) High carbohydrate diets inhibit efficient lipid delivery to the brain, inhibiting function of glucose transporters and lowering acetyl-CoA pools. (**II**) Low EFA and acetyl-CoA levels inhibit cholesterol metabolism and membrane function and integrity. (**III**) Inability to maintain lipid homeostasis results in improper processing of APP and Aβ generation. Premature cleavage of APP results in failure to deliver neurotrophin receptors to cell surface and cell death. (**IV**) Accumulation of toxic Aβ. Abbreviations: EFA — essential fatty acid, MCTr — monocarboxylate transporter, KB — ketone bodies.

lular trafficking [72]. Failure to deliver neurotrophin receptors would lead to widespread neuronal cell death (Fig. 4, for review see [73]). In fact, inhibiting NGF in the brains of mice results in an age dependent pathology very similar to AD [74].

Stage I/II — insulin/IGF signaling and aging

HC diets are well known to increase glucose and insulin levels in humans [31] and this elevated insulin signaling may lead to rapid aging of susceptible tissues. In mammals and lower organisms there is growing evidence that insulin/IGF signaling modulates lifespan (for overview see [75]). For example, reducing the caloric intake of mice and rats reduces insulin/IGF levels and increases life span (for review see [76]). More direct evidence comes from the observation that mice heterozygous for the IGF-1 receptor live ~33% longer than their wild-type littermates [77] and mice lacking the insulin receptor in fat cells live ~18% longer [78].

The insulin-like signaling pathway shows remarkable conservation across phyla. In both nematodes and mammals insulin/IGF signaling negatively regulates the activity of the Foxo family of transcription factors by sequestration in the cytoplasm (for review see [79,80]). Activation of Foxo proteins increases stress resistance and longevity in mice and nematodes [75]. The long-lived p66shc(−/−) mouse may have increased Foxo activation and increased resistance to oxidative stress [81]. Activation of FKHR (a Foxo protein) increases expression of stress response genes, such as Gadd45a, a gene involved in DNA repair [82]. It has been proposed that insulin/IGF signaling functions, via Foxo proteins, to adjust metabolism and ultimately lifespan in response to nutritional and environmental cues [83,84]. Low food availability will increase the proportion of Foxo in the nucleus and increase the expression of a variety of stress resistance genes, resulting in more stress resistant longer lived individuals. High food availability will decrease the expression of stress genes, resulting in less stress resistant shorter lived individuals.

The mammalian brain is well supplied with insulin receptors where insulin appears to signal abundant food and not trigger glucose uptake as it does in muscle and fat [85,86]. For example, chronic infusion of insulin into the brains of baboons reduces food intake [87], while inhibition of the insulin receptor in the brains of mice increases food intake [88,89]. Therefore, the strong increases in postprandial glucose and insulin levels induced by HC diets may continuously signal that nutrients are plentiful, exclude Foxo from the nucleus, and accelerate aging of susceptible neurons (Fig. 3(***VI***)). This condition will be exacerbated in E4 individuals who are more insulin sensitive.

Treatment and prevention

This hypothesis suggests several treatment and preventative measures that may be beneficial for AD and other disorders resulting from what can be collectively called the "Neolithic Syndrome". Such treatment may be especially effective in combination.

The Paleolithic prescription

A modified "Paleolithic prescription" [90] may prevent AD. The Paleolithic prescription proposes a change in diet and activity to a level more similar to our Late Paleolithic ancestors, and emphasizes reducing fat and increasing dietary fiber as the keys to better health [90,91]. However, the inhibition of lipid metabolism by HC diets may be the most detrimental aspect of modern diets. Therefore, reducing dietary intake of high-glycemic carbohydrates and increasing protein, fiber and fat would be preferred. Similar diets appear to reduce the risk of AD [92]. Since HC diets are proposed to be the primary cause of AD regardless of apoE genotype, such a diet would generally reduce the risk of AD. However, this diet is predicted to be particularly beneficial to carriers of apoE4, and suggests that individuals should "eat right for your apoE type". Dietary change would be the preventative treatment of choice, since it would not only lower the incidence of AD, but many other harmful conditions. Yet such a change would require dramatic decreases in carbohydrate intake (to < 30% of daily caloric intake) and would be difficult to implement without drastic changes in dietary thinking.

EFA repletion diet

Increasing evidence has implicated consumption of fish (a source of EFA) as protective against AD [50]. For individuals in Stage I or II, an EFA repletion regime, consisting of high doses of EFA, may replenish EFA in neuronal membranes and prevent and/or treat the disease [93]. In particular, elevation of $n-3$ EFA may allow for more efficient

function of glucose transporters and the APP protein.

Ketone body treatment

While increasing fatty acid metabolism may help prevent the disease, by the time clinical dementia is diagnosed (Stage II) irreparable damage may have occurred and reversal will be difficult. One strategy that might be effective is direct elevation of acetyl-CoA levels using ketone bodies (KB). Increasing acetyl-CoA levels will provide a substrate for acetylcholine and cholesterol synthesis and can be used in the TCA cycle [94]. A simple way to elevate plasma KB levels is through consumption of medium chain triglycerides, which are readily metabolized to KB. We have found that exogenous administration of medium chain triglycerides increased cognitive performance in early stage non-E4 AD patients [95].

Increasing fatty acid metabolism

Drugs that increase the use of fatty acids, especially in glia, may be beneficial for AD. This may explain the beneficial effects of statins (as discussed) and non-steroid anti-inflammatory drugs (NSAIDS) [96]. NSAIDS function, in part, as PPAR-gamma agonists. Increasing PPAR-gamma activity increases the expression of genes associated with fatty acid metabolism such as FATP (for review see [97]). Other drugs may have similar effects. Fibrate drugs, such as Bezafibrate, ciprofibrate, fenofibrate and Gemfibrozil may also prove beneficial. Fibrates act as PPAR-alpha agonists and like statins they increase lipoprotein lipase, apoAI and apoAII transcription and reduce levels of apoCIII, thereby increasing lipid availability to the brain [98].

Conclusion

AD is a devastating neurodegenerative disorder that will reach epidemic proportions in the next 50 years. While tremendous progress has been made in our molecular understanding of the disease, no effective treatments exist. Much of the current research centers on modulating the processing of the APP protein and correcting the imbalance between Aβ production and clearance. This approach, while promising, has many drawbacks. Altering the processing of APP may affect other proteins such as Notch and is technically difficult [99]. Here it is argued that the primary event leading to the development of AD is consumption of an evolutionarily discordant HC diet. This hypothesis predicts that relatively simple preventative measures, such as lowering the consumption of starchy carbohydrates and increasing EFA in the diet will be effective. Yet, in practice this may be difficult without sufficient public awareness. Other treatments may also be effective, such as ketone body therapy, EFA repletion diets, and statin drugs. Hopefully, in the future more research will focus on the role of diet in AD.

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