Is There a Link between Saturated Fat Intake and Alzheimer's disease?

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Abstract
Alzheimer's disease is a neurodegenerative disease that causes dementia and ultimately death. Currently, there is no treatment available for this disease. The aging of the population will only increase the incidence of Alzheimer's disease, making it ever more important to find an effective method of prevention. Dietary intervention is a practical and affordable method of intervention. The brain is a fat rich organ, and dietary fats are critical for proper development of the brain. A literature review was conducted to determine whether there is a link between saturated fat intake and Alzheimer's disease. According to the literature reviewed, saturated fat increases the amount of amyloid beta in circulation, and is linked to blood brain barrier dysfunction. Consistent with this, high saturated fat diets lead to cognitive decline in animals. Epidemiologic studies have yielded conflicting results, but most studies show a link between increased intake of saturated fat and increased incidence of Alzheimer's disease. Lipid lowering agents and anti-inflammatory drugs have been found to attenuate the effect of a high saturated fat diet in animals. An examination of medical records has also shown that patients who had been prescribed statins were less likely to be afflicted with Alzheimer's disease. The literature reviewed indicates that lowering intake of saturated fat as part of a healthy diet may reduce the risk of Alzheimer's disease later in life. There is also evidence that lipid lowering agents and anti-inflammatory drugs may slow the progression of Alzheimer's disease.

Introduction

Alzheimer's disease is a neurodegenerative disease that causes severe memory loss and ultimately death. The first part of the brain affected by Alzheimer's disease is the hippocampus, a region of the brain associated with memory. Memory loss is usually the first symptom of Alzheimer's disease. As the disease progresses the degeneration spreads to other parts of the brain leading to the loss of other cognitive skills such as language skills and the ability to plan. Eventually, damage to the basal nucleus of Meynert leads to a sharp drop in the amount of the neurotransmitter acetycholine present in the brain, leading to further deficiencies (Peterson, 2002). Approximately ten percent of the population over the age of 65 and fifty percent of those above 85 suffer from Alzheimer's disease (Carlson, 2011). Currently, there is no medication that can cure Alzheimer's disease or stop its progression. Patients suffering from Alzheimer's disease are treated with medications that alleviate the symptoms. Acetylcholinesterase inhibitors are prescribed to alleviate the cognitive symptoms. Anxiolytics and antipsychotics may be prescribed to treat behavioral symptoms. These drugs, however, may worsen cognitive deficiencies. Ultimately, the inexorable progression of Alzheimer's disease leads to death (Peterson, 2002).

Although the cause of Alzheimer's disease has not been definitively determined, two pathological conditions have been linked to Alzheimer's disease, amyloid plaques and neurofibrillary tangles. The amyloid plaques are extracellular deposits of the protein beta amyloid (sometimes referred to as amyloid beta). These plaques are surrounded by degenerating neurons and activated microglia, the phagocytotic cells of the central nervous system. Activated microglia are a sign of inflammation or immune response. The neurofibrillary tangles are intracellular accumulations of hyperphosphorylated tau proteins. These tangles disrupt transport within the neurons eventually killing the cell and leaving behind the tangle of filaments (Carlson, 2011).

Alzheimer's disease is split into two categories: early onset, also called familial, and late onset, also called sporadic. Alzheimer's disease occurring before the age of 65 is considered familial whereas Alzheimer's disease occurring after the age of 65 is considered sporadic. Familial Alzheimer's shows a clear pattern of inheritance. In different families the disease is caused by different genetic mutations. Three genetic mutations have been identified: a mutation in the amyloid precursor protein gene (APP) gene, a mutation in the presenilin 1 (PS1) and a mutation in the presenilin 2 (PS2) gene. All three of these mutations have been shown to increase the relative amount of amyloid beta 42 in the brain. Amyloid beta 42 is "stickier" than the wild type variant, amyloid beta 40. Consequently, amyloid beta 42 is more likely to conglomerate and form plaques. Sporadic or late onset Alzheimer's disease does not show any clear pattern of inheritance. However, a variant of the apolipoprotien E gene, apolipoprotein epsilon 4, has been linked to increased occurrence and earlier age of onset of Alzheimer's disease. Apolipoprotein E is a carrier protein for cholesterol. The epsilon 4 variant of this protein has been linked to an increase in the amount of amyloid beta in the brain. The mechanism behind this relationship is unknown. Researchers suspect that apolipoprotein E is involved in the clearance of amyloid beta from the brain and that the epsilon 4 variant is not as effective the epsilon 2 or epsilon 3 variants in clearing amyloid beta (Peterson, 2002).

Researchers have recently begun to examine the role of diet in the etiology of this disease (Heude et al 2003, Kalmijn et al 1997, Engelhart et al 2002, Luchsinger et al 2002, Morris et al 2003 and Laitnen et-al 2006). Diet is a particularly interesting field for research because dietary interventions are relatively cheap and easy to initiate. This research hopes to provide the public with a cost effective method for preventing Alzheimer's disease, or at least delaying its onset. Dietary fats in particular have been the focus of much research. The central nervous system has a

very high concentration of lipids, second only to adipose tissue. Additionally, lack of essential fatty acids has been shown to be a limiting factor in brain development (Winocur and Greenwood, 1993). It follows that intake of fatty acids would have a significant impact on the health of the brain later in life. The link between apolipoprotien E and Alzheimer's disease also suggests a role for lipid metabolism in the etiology of Alzheimer's disease.

Dietary fatty acids are ingested as triglycerides, groups of three fatty acids attached by an ester bond to a glycerol backbone. In the small intestine, these triglycerides are broken down to monoglycerides and fatty acids by the enzyme lipase. After being absorbed by the epithelial cells of the small intestine, they are recombined to form triglycerides. Because triglycerides are not water soluble, they cannot be transported through the blood stream without a carrier. Instead, they are combined with proteins to form lipoproteins. Lipoproteins are spherical particles with an outer shell of proteins, phospholipids and cholesterol surrounding an inner core of triglycerides. There are a number of different types of lipoproteins, each with a different composition and a different function. The lipoprotein formed in the epithelial cells of the intestine is called a chylomicron. The chylomicron passes from the intestinal epithelial cells to the lacteal, and is delivered to the blood stream via the lymph system (Tortora and Derrickson 2006).

Studies have shown that rats raised on a diet high in saturated fat were impaired on behavioral tests (Winocur and Greenwood 1993). Changes in the morphology of the hippocampus consistent with a loss of dendritic integrity and immune response were also observed (Granholm et al 2008). Additionally, animals that were fed a diet high in saturated fat were found to have higher concentrations of the protein amyloid beta (Galloway et al 2007), the main component of amyloid plaques, and compromised blood brain barrier integrity (Farrall and Wardlaw 2009, Taketchi et al 2010, Taketchi et al 2013a, Taketchi et al 2013b, and Freeman and Granholm 2012). In humans, however, the link between saturated fats and Alzheimer's is not as clear. A number of studies have been conducted, and they have yielded conflicting results. This paper will review and elucidate the relevant research with the goal of answering the following two questions: Is there a definitive link between high intake of saturated fat and incidence of Alzheimer's disease? If yes, what is the mechanism of this relationship, and does this suggest any possible interventions other than diet modification?

Methods

A literature search was conducted using pubmed.gov. The following search terms were used: Alzheimer's disease AND saturated fat, Alzheimer's disease AND dietary fat, Alzheimer's disease AND amyloid beta, Alzheimer's disease AND blood brain barrier, and Alzheimer's disease AND statins. To exclude irrelevant papers the search terms were restricted to the title and abstract. Of the papers that were found using these search terms, relevant papers were selected based on their abstract. Additional sources of information were found in the reference sections of these papers.

Discussion

Saturated Fat and Amyloid Beta

In 1992 Hardy and Higgins proposed that the deposition of amyloid plaques is the initiating event in Alzheimer's disease. This hypothesis, called the amyloid cascade hypothesis, suggests that an influx of calcium caused by the toxic effects of amyloid plaques leads to hyperphosphorylation of the tau proteins which then form neurofibrillary tangles and kill the neurons. A number of findings support this theory. Firstly, it has been observed that mutations of the gene encoding the tau protein lead to Parkinson's-like symptoms, but did not lead to the deposition of amyloid plaques. Secondly, it has been observed that mice expressing mutant variations of both amyloid beta and tau protein experience increased formation of tau protein tangles when compared to mice expressing only the mutant version of tau protein, while the number of amyloid plaques is the same. Both of these observations indicate that the deposition of amyloid plaques leads to the formation of tau protein tangles, but not the other way around. The discovery that familial Alzheimer's disease is caused by a genetic mutation in the amyloid precursor protein also supports the amyloid cascade hypothesis. It seems likely that both familial and sporadic Alzheimer's disease share an underlying cause (Hardy and Selkoe, 2002).

It has been shown that the degree of dementia is correlated with the amount of amyloid beta present in the brain (Naslund et. al. 2000). However, there is no evidence of increased production of the amyloid beta protein in the brains' of Alzheimer's disease patients, indicating that the observed increase is caused by decreased clearance of amyloid beta from the brain or increased uptake of this protein from circulation (Pallebage-Gamarallage et. al. 2009). Using iodine-125 labeled amyloid beta, researchers have shown showed that amyloid beta from circulation does indeed cross the blood brain barrier (Mackic et. al. 2002) This suggests that factors which increase the levels of circulating amyloid beta may increase the level of amyloid beta in the brain, and lead to the formation of plaques.

The protein amyloid beta is involved in the metabolism of lipids. In vivo, it is associated with chylomicrons and lipoprotein B, and it increases the uptake of triglyceride rich lipoproteins (TRLs) by fat rich organs (James et. al. 2003). Consistent with this, it has been found that a diet high in saturated fat increases the levels of amyloid beta in enterocytes (Galloway et. al. 2007). The link between lipid metabolism and the deposition of amyloid plaques

in the brain is further strengthened by the finding that high serum cholesterol induced by high cholesterol feeding is correlated with increased levels of amyloid beta in the brain, as well as increases in the number and size of amyloid plaques (Refolo, 2000). These studies investigated the effect of cholesterol only, but not the effect of saturated fat.

The link between saturated fat and amyloid plaques suggests that reducing intake of saturated fat would reduce the incidence of Alzheimer's disease. However, it must be noted, that a ketogenic diet, a diet very low in carbohydrate content and very high in fat content, has been shown to lower the amount of amyloid beta in a rat's brain (Van der Auwera et. al. 2005). This indicates that the increase in amyloid beta observed in rats fed a high saturated fat diet is not simply because of the high fat content. Rather, it is the result of a synergistic effect between saturated fats and carbohydrates.

Saturated Fat and Blood Brain Barrier Dysfunction

Saturated fat may also have a detrimental effect on the health of the brain by disrupting the blood brain barrier. The blood brain barrier was discovered more than 100 years ago by Paul Ehrlich when he observed that blue dye injected into an animal's blood stream will not reach the spinal cord or the brain. The blood brain barrier is formed by the endothelial cells of the blood vessels in the central nervous system. In most capillaries there are gaps between the endothelial cells that allow substances to diffuse in and out of the blood. In contrast, the endothelial cells in the central nervous system are tightly packed, and held together by tight junctions. This prevents many substances that normally diffuse out of the blood stream from diffusing into the central nervous system (Carlson, 2011).

A disruption of the blood brain barrier can lead to Alzheimer's disease through two distinct pathways. As previously mentioned, there is evidence that the increase in the amount of amyloid beta in the brains of Alzheimer's patients may be due to an influx of amyloid beta from circulation. We previously explored the possibility that this is because intake of certain lipids increases the amount of amyloid beta present in the blood. Another possibility is that the influx of amyloid beta is due to the breakdown of the blood brain barrier. In addition to affecting the level of amyloid beta in the brain, a breakdown of the blood brain barrier would allow toxins to enter the brain, possibly leading to Alzheimer's disease through a completely different pathway.

There are a number of methods by which blood brain barrier integrity can be assessed. The levels of plasma derived proteins in the brain can be measured, with a greater amount indicating influx through the blood brain barrier. Similarly, the levels of cerebrospinal fluid derived proteins in the plasma can also be measured to determine efflux through the blood brain barrier. Immunoflourescent antibodies can be used to detect the presence of tight junction proteins and other proteins integral to the maintenance of the blood brain barrier. Imaging techniques such as contrast CT, contrast MRI, and positron emission topography (PET) have also been used.

Whether blood brain barrier dysfunction is linked to Alzheimer's disease has been debated for many years. A number of experiments have been performed using both biochemical and imaging techniques. A meta-analysis of sixteen studies found that there was a statistically significant link. There was, however, great heterogeneity among the results of individual studies (Farrall and Wardlaw, 2009).

To examine the effects of saturated fat on the blood brain barrier, researchers examined the brains of mice fed a diet high in saturated fat, high in unsaturated fat and a control group fed standard laboratory chow. Immunoglobin G (IgG), and apolipoprotien B (a hepatically derived lipoprotein) were used to measure influx. The cerebrospinal fluid protein, S100B was used to detect efflux. After three months, the mice were euthanized, and the relative abundance of occludin, a tight junction protein, was also assessed. It was observed that levels of immunoglobin G and apolipoprotien B were greatly elevated in the brains of mice in the saturated fat group, indicating increased influx of proteins and lipoproteins. The increased presence of apolipoprotein B, a lipoprotein that is associated with amyloid beta in enterocytes, supports the theory that blood brain barrier dysfunction can cause Alzheimer's disease by increasing the influx of amyloid beta. Plasma levels of S100B were also greatly elevated indicating efflux from the cerebrospinal fluid into the brain. Finally, levels of occludin were found to be lower in the saturated fat group, indicating a breakdown of the tight junctions that form the blood brain barrier. The effects of the high saturated fat diet were exacerbated when the mice were examined after six months of feeding (Taketchi et. al. 2010 and Taketchi et. al. 2013a).

Another experiment examined the effect of a high saturate fat/high cholesterol diet on three blood brain barrier proteins. The proteins investigated were endothelial barrier protein and the tight junction proteins occludin, and ZO-1. Using immunoflourescent antibodies the high saturated fat/high cholesterol fed rats were found to have markedly less endothelial barrier protein in the cortex and the CA-1 region of the hippocampus. When analyzed by western blot, a hippocampal homogenate of the experimental rats was found to have more occludin and the same amount of ZO-1 as that of the control rats. However, immunoflourescent imaging showed that the localization of occludin was markedly different in the two groups. In the control group

occludin was found to be present mostly in the walls of blood vessels, as would be expected for a blood brain barrier protein. In contrast, the blood vessels of the experimental group stained very weakly for occludin, while there was a strong signal in axon fibers and granule cells of the dentate gyrus. It may be that the increased level of occludin detected in the brain of the experimental group was because expression of occludin had been up-regulated in response to blood brain barrier damage (Freeman and Granholm, 2012).

Saturated Fat and Cognitive Decline in Animals

The evidence linking saturated fat to increased production of amyloid beta and blood brain barrier dysfunction suggests a link between saturated fat and Alzheimer's disease. Indeed, a link between saturated fat and cognition has been observed in rats. Researchers found that rats fed a diet high in saturated fat performed worse on memory tests than rats fed a diet that had unsaturated fat as its main fat component (Winocur and Gordon 1993). Again, it must be noted that rats fed a ketogenic diet did not experience any cognitive decline, despite the extremely high saturated fat content in their diets. This is consistent with the finding that a ketogenic diet reduces the levels of amyloid beta in the brain (Van der Auwera et al 2005).

In addition to memory impairment, researchers found that a diet high in cholesterol and saturated fat significantly altered the morphology of the hippocampus, one of the areas of the brain responsible for memory and learning. After being fed a diet high in saturated fat and cholesterol, sections of the hippocampus were tested for Map2, an integral membrane protein that is considered a marker for dendrites, and Iba1 a marker for microglia. Compared to the control group, rats fed a diet high in saturated fat had significantly less Map2 and considerably more Iba1, indicating a loss of dendritic integrity and activation of microglia, both hallmarks of Alzheimer's disease (Granholm et al 2008).

Saturated Fat and Alzheimer's Disease

A link between saturated fat and Alzheimer's disease cannot be definitively asserted unless there is evidence of such a link in humans. A number of epidemiologic studies have been conducted to determine the link between dietary fats and Alzheimer's disease (Heude et. al. 2003, Kalmijn et. al. 1997, Engelhart et. al. 2002, Luchsinger et. al. 2002, Morris et. al. 2003, and Laitnen et. al. 2006). Although the information gleaned from these studies is enlightening, the results must be approached with caution. All of these studies rely on self reporting. Because participants do not know how much fat they have ingested, researchers use food frequency questionnaires that ask participants about their dietary habits. This information is used to estimate their intake of various micronutrients. This method is an estimate at best. As with all studies relying on self reporting there is an inherent inaccuracy. Additionally, responses on a questionnaire reflect only the respondent's current diet, but offer no information about their dietary habits in the past. Discrepancies among these studies can arise from differences in the questionnaires used, length of follow up time, the age of the population being studied, and the ethnicity of the population.

In the Rotterdam study, 7,983 residents of a suburb of Rotterdam over the age of 55 were administered questionnaires that were followed up by clinical examinations. After a two year follow up, researchers found a statistically significant link between increased intake of saturated fat and incidence of Alzheimer's disease (Kalmijn et. al. 1997). Interestingly, the link was significant even after eliminating patients with cerebrovascular disease, indicating that the mechanism mediating this link is not vascular in nature. However, a six year follow up of the same group showed no significant link between saturated fat intake and Alzheimer's disease (Engelhart et. al. 2002). An examination of the methods used in the two studies does not reveal an obvious reason for this discrepancy. Both studies used the same method of assessing dietary intake of fats, and both adjusted their results for similar confounding variables. The authors of the second study do not address the discrepancy directly, but they do suggest that the longer follow up may introduce selective survival. For instance, it may be that subjects who live longer are less susceptible to the detrimental effects of a high fat diet leading to a longer life span, and a lower incidence of dementia as well (Engelhart et. al. 2002). It may also be that saturated fat lowers the age of onset of Alzheimer's disease, but does not increase overall incidence.

Using data from the Washington Heights-Inwood Columbia Aging Project (WHICAP), researchers found a link between total intake of fat and increased incidence of Alzheimer's disease. Saturated fat alone was linked to increased incidence of Alzheimer's disease; however, the hazard ratio was slightly lower than that of total fat intake and was less than that of monounsaturated fats, indicating that saturated fat is not more harmful than other fats. Although increased intake of saturated fat overall was linked to increased incidence of Alzheimer's disease, no difference was found between those reporting moderately high intake and those reporting very high intake. When the data was analyzed using only people who had tested positive for the apolipoprotien E epsilon 4 allele (both homozygous and heterozygous) the link between total fat intake and Alzheimer's disease was much stronger and successively greater intake of saturated fat indicated successively greater risk of Alzheimer's disease (Luchsinger et al 2002).

Another study using data from the Chicago Aging Project and a median follow up of 3.9 years found a strong link between saturated fat and Alzheimer's disease. Participants in the top fifth of saturated fat intake were 70% more likely to develop Alzheimer's

disease. This is in contrast to other fats, some of which seemed to lower the risk of Alzheimer's disease. Adjusting for confounding variables led to 120% increase in risk. In contrast to the findings of Luchsinger et al (2002), this study found that the link between saturated fat and Alzheimer's disease was not any stronger in participants possessing the apolipoprotein E epsilon 4 allele (Morris et al 2003).

The previous studies focused on elderly people and had a follow up between two and seven years. A short follow up can potentially underestimate the link because of the possibility of subclinical dementia (i.e. the patients who were discovered to have dementia might have had subclinical dementia at baseline, and the poor diet is a symptom rather than a cause of the disease). In contrast, Laitnen et al (2006) studied the link between fat intake at midlife and the incidence of Alzheimer's disease later in life. In this study participants of the CAIDE study who had been examined in either 1972, 77, 82, or 87 were called for reexamination in 1998. The mean follow up was 21 years. This study found that participants with moderate fat intake (second quartile) had a lower risk of Alzheimer's disease than either low fat or high fat intake. When broken down to specific fats, high polyunsaturated fats and monounsaturated fats were correlated with a decreased risk of Alzheimer's disease, while high intake of saturated fats was correlated with a higher incidence of Alzheimer's disease. Only the data for polyunsaturated fats and saturated fats yielded results that were statically significant. When adjusted for the Apolipoprotien E epsilon 4 allele, the results were similar; suggesting that effect of saturated fat is not related to the Apolipoprotein E epsilon 4 allele. It is noteworthy that this study calculated relative intake of fatty acids based only on intake of different types of dairy, excluding two major sources of dietary fatty acids, meat and fish.

As previously mentioned, studies that rely on self reporting food frequency questionnaires are inherently inaccurate. To address this problem, researchers studied the link between erythrocyte membrane content and cognitive decline. This study found a significant link between saturated fatty acid content in erythrocytes and cognitive decline. Interestingly, the results for polyunsaturated fatty acids were mixed; n-6 polunsaturated fatty acids were linked to cognitive decline while n-3 polyunsaturated fatty acids seemed to protect against decline. This study investigated only the link between fatty acids and general cognitive decline. A link between membrane composition and Alzheimer's disease specifically was not investigated (Heude et al 2003).

Lipid-Lowering Pharmaceuticals

The link between saturated fatty acids and Alzheimer's disease suggests that drugs that lower plasma lipids may prevent Alzheimer's disease, or slow its progression. Probucol is a lipid-lowering agent with anti-inflammatory and antioxidant properties that has been used to treat cardiovascular disease (Santos, 2012). Experiments with mice have shown that Probucol ameliorates the detrimental effects of a diet high in saturated fat. It was previously mentioned that mice fed a diet high in saturated fat and cholesterol were found to have a greater abundance of the protein amyloid beta in enterocytes. When Probucol was added to their diet, the levels of enterocytic amyloid beta in the saturated fat group were comparable to those in the control group (Pallebage-Gamaramllage et al 2012).

It was also found that Probucol prevented the damage to the blood brain barrier normally associated with a high saturated fat diet. Mice were randomly assigned either to a control diet, a diet high in saturated fat, a diet high in cholesterol, or a high saturated fat/high cholesterol diet with Probucol for three months. Consistent with previous experiments the mice in the high saturated fat and high cholesterol diets were found to have damage to the blood brain barrier as measured by the concentrations of immunoglobin G and apolipoprotien B in the brain, and the concentration of S100B in the blood plasma. High saturated fat and high cholesterol mice were also found to have a greater abundance of activated microglia, a sign of inflammation. However in mice treated with Probucol the levels of immunoglobin G, apolipoprotein B and S100B were comparable to that of the control group. There was also no evidence of inflammation in mice treated with Probucol (Taketchi et al 2013a).

When the experiment was repeated and mice were kept on the high saturated fat diets for 12 months the effect of the high saturated fat diet on blood brain barrier permeability and enterocytic abundance of amyloid beta was even more pronounced. Yet, despite the long term exposure to saturated fat, the group treated with Probucol was not effected (Taketchi et al 2014). In addition to preventing damage to the blood brain barrier and lowering enteroctyic accumulation of amyloid beta, Probucol was also found to increase synaptic density in mice (Poirier, 2008).

A pilot study examined the effect of Probucol on 12 patients with mild-to-moderate Alzheimer's disease. A clinical assessment after six months of treatment found that Probucol led to a stabilization of symptoms (Poirier, 2008). This was a small scale study that did not include a control group. A long term controlled study is needed to definitively determine whether Probucol is an effective treatment for Alzheimer's disease and whether its effect is long lasting.

It is possible that the positive effects of Probucol are not related to lipid metabolism. Probucol was found to attenuate the effects of an injection of amyloid beta in mice. Mice injected with amyloid beta exhibited cognitive decline, and a histological examination of

their brains shows decreased synaptic density (as measured by the presence of the presynaptic protein synaptophysin) and increased acetylcholinesterase activity. Injection with amyloid beta does not increase plasma cholesterol. Treatment with Probucol for 15 days attenuated the effects of the amyloid beta injection. This is despite the fact that the pathological conditions observed in these mice were not due to increased lipid intake or dysfunctional lipid metabolism. This suggests that Probucol may directly affect the pathway responsible for Alzheimer's disease pathology in addition to its positive effect on lipid metabolism (Poirier, 2008).

Statins (HMGCoA reductase inhibitors) are another group of lipid lowering agents prescribed to treat cardiovascular disease. Similar to Probucol, statins also have anti inflammatory properties. In an experiment similar to that performed with Probucol it was shown that treatment with statins will reverse the blood brain barrier damage caused by a high saturated fat diet. Mice were fed either a low fat diet or a diet high in saturated fat. Consistent with previous experiments the mice fed a diet high in saturated fat were found to have significantly higher levels if immunoglobin G and apoliprotien B in the brain parenchyma, an indication of blood brain barrier damage. Treatment for two weeks with Atorvastatin, a lipid soluble statin, led to a decrease in the amount of immunoglobin G present in the brain. Treatment with pravastatin, a water soluble statin did not lead to any reduction after two weeks. After eight weeks of treatment it was found that both atorvastatin and pravastatin completely negated the effects of the high saturated fat diet (Pallebage-Gamarallage et al 2012). Unlike other studies, this study tested the effect of the experimental compound after the mice had been on the saturated fat diet for an extended period of time. The effectiveness of the compounds after the effects of the saturated fat diet had presumably set in suggests that statins may be effective at reversing damage to the blood brain barrier as opposed to simply preventing it.

An analysis of data obtained from the General Practice Research Database in the UK revealed that individuals who had been prescribed statins had a significantly reduced incidence of Alzheimer's disease. This was true even for individuals who had taken statins in the past, but were no longer taking these drugs. Interestingly, use of other lipid lowering agents was not correlated with a lower risk of Alzheimer's disease (Jick et al 2000). Another study used data from the databases of three different U.S. hospitals. This study also found a statistically significant relationship between use of lovastatin (Mevacor) or pravastatin sodium (Pravachol), and a lower incidence of Alzheimer's disease. Simvastatin (Zocor), a different statin, was not correlated with decreased incidence of Alzheimer's disease in this study (Wolozin et al 2000).

Ibuprofen, a non-steroid anti inflammatory drug (NSAID) that does not have any lipid lowering properties was also tested alongside simvastatin and pravastatin in the previously described experiment. After two weeks of treatment Ibuprofen was found to be as effective as simvastatin, and eight weeks of treatment completely reversed the effects of the high saturated fat diet (Pallebage-Gamarallage et al 2012). Antioxidants are another group of compounds that have been found to ameliorate the effect of saturated fat. Inflammation is caused by reactive oxygen species (ROS). Anti oxidants combat the effects of reactive oxygen species and prevent inflammation. Four compounds were tested: aged garlic extract, alpha-lipoic acid, niacin, and nicotinamide. Mice were fed either a low fat diet a high saturated fat diet or a high saturated fat diet containing one of the four compounds. All four compounds were found to prevent the blood brain barrier dysfunction and inflammation caused by a high saturated fat diet (Takechi et al 2013b). These studies suggest that the protective property of statins and Probucol that was observed in humans and mice may be related to their anti inflammatory properties and not their lipid lowering properties.

Conclusion

Saturated fat is clearly linked to an increase in amyloid beta and to blood brain barrier dysfunction in animals. Although not definitive, epidemiologic evidence seems to indicate that increased intake of saturated fat is a risk factor for Alzheimer's disease. Based on the evidence presented, it is reasonable to suggest limiting intake of saturated fat as part of an effort decrease the risk of Alzheimer's disease. In particular those with the apolipoprotein E epsilon 4 allele should limit their intake of saturated fat. However, it must be noted that saturated fat is only one among many micronutrients that make up our diet. Saturated fat alone is not responsible for inflammation, blood brain barrier dysfunction, or deposition of amyloid plaques. In fact, we have cited evidence that a ketogenic diet, which is high in saturated fat, reduces the amount of amyloid beta in the brain. When designing a diet low in saturated fat one needs to ensure that saturated fat is not replaced with an equally unhealthy substitute. Furthermore, there is no evidence that limiting saturated fat intake after the onset of Alzheimer's disease will reverse or even slow the disease's progression. At best, limiting intake of saturated fat throughout the course of one's life will lower the incidence of Alzheimer's disease and delay its onset, but it will not cure it.

The use of Probucol, statins, and other anti-inflammatory medications in the treatment of Alzheimer's disease is strongly supported by the evidence cited. Anti inflammatory medication has been shown to reverse damage to the blood bran barrier caused by saturated fat. Probucol has been shown to lower enterocytic accumulation of amyloid beta and to slow the progression of Alzheimer's disease. Use of statins has also been linked

to a decreased risk for Alzheimer's disease. Further research is needed to determine which of these drugs is most effective, and whether these drugs can be effective in the long term.

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