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Intersection Between Metabolic Dysfunction, High Fat Diet Consumption, And Brain Aging

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Abstract

Deleterious neurochemical, structural, and behavioral alterations are a seemingly unavoidable aspect of brain aging. However, the basis for these alterations, as well as the basis for the tremendous variability in regards to the degree to which these aspects are altered in aging individuals, remains to be elucidated. An increasing number of individuals regularly consume a diet high in fat, with high fat diet consumption known to be sufficient to promote metabolic dysfunction, although the links between high fat diet consumption and aging are only now beginning to be elucidated. In this review we discuss the potential role for age-related metabolic disturbances serving as an important basis for deleterious perturbations in the aging brain. These data not only have important implications for understanding the basis of brain aging, but also may be important to the development of therapeutic interventions which promote successful brain aging.

Keywords

Aging; Brain; Diabetes; Insulin Resistance; Neurodegeneration; Metabolism; Obesity

What causes the brain to age?

Aging is a largely hypothetical construct that has a wide range of working definitions. For example, aging can be defined as the collection of changes that increase over time to promote morbidity and consequently render individuals progressively more likely to die (Medawar PB 1952). Alternatively, aging has been defined as a gradual deterioration of physiological function with age (Partridge and Mangel 1999). With regards to the aging of tissues, aging can be defined as an intrinsic and potentially irreversible set of processes which result in a loss of viability and increased vulnerability (Comfort A 1964). With specific regards to the brain, it is well established that as the result of increased chronological aging the brain undergoes numerous alterations at the molecular, cellular, and structural level. In this review we will discuss the potential roles of metabolic perturbations such as obesity and insulin resistance, serving as modulators for multiple aspects of brain aging. Additionally, the links between high fat diet consumption and metabolic dysfunction are discussed in the context of brain aging.

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Molecular and cellular changes in the aging brain

In regards to brain aging some of the most studied molecular and cellular changes can be grouped as being alterations in neurotransmitter signaling, increases in inflammatory signaling, and increases in oxidative stress (Fig. 1). Each of these is discussed below and in later sections discussed in the context of age and diet-induced metabolic dysfunction.

Changes in neurotransmitter signaling within the aging brain

In the aging brain there are well documented changes in multiple aspects of neurotransmitter signaling. For example, declines in the levels of neurotransmitters such as acetylcholine are well documented in the aging brain (Bartus *et al.* 1982;Gibson and Peterson 1981;Gibson *et al.* 1981;Ogawa 1989;Terry, Jr. and Buccafusco 2003;Vannucchi and Pepeu 1987;Wu *et al.* 1988) and age-related neurodegenerative disorders such as Alzheimer's disease (AD) (Bartus *et al.* 1982;Ogawa 1989;Terry, Jr. and Buccafusco 2003;Jia *et al.* 2004;Tohgi *et al.* 1994). Additionally, the levels and density of key neurotransmitters such as dopamine have been demonstrated to be decreased in the aging brain (Bannon and Whitty 1997;Carlsson 1987;Meng *et al.* 1999;Volkow *et al.* 1996;Wang *et al.* 1998). In contrast, studies indicate a role for excessive glutamate signaling occurring in the aging brain, especially in age-related disorders such as AD, culminating in the development of neuron death through excitotoxicity (Coyle *et al.* 1981;Coyle and Puttfarcken 1993;Hynd *et al.* 2004;Mattson *et al.* 1992;Mattson *et al.* 1995b;Mattson *et al.* 1995a;Sattler and Tymianski 2000). Together, these data point to gross imbalances in neurotransmitters occuring during brain aging and age-related diseases of the brain.

In addition to having an imbalance in the level of neurotransmitters within the brain, additional studies have documented that there is a deleterious change in the levels of key neurotransmitter receptors during aging. For example, it has been demonstrated that the glutamate receptor subunits (NR1, NR2A, and NR2B), and the AMPA receptor decline with age (Adams *et al.* 2008;Clark *et al.* 1992;Gazzaley *et al.* 1996;Morrison and Hof 1997;Sonntag *et al.* 2000;Wenk and Barnes 2000;Magnusson 2000;Eckles-Smith *et al.* 2000;Clayton and Browning 2001;Clayton *et al.* 2002;Shi *et al.* 2007;Newton *et al.* 2008). Similarly, a number of studies have also reported significant age-related decreases in the levels of dopamine receptors D1, D2, and D3 (Wang *et al.* 1998;Kaasinen *et al.* 2000;Iyo and Yamasaki 1993;Rinne *et al.* 1990;Wong *et al.* 1984). Decreasing levels of different serotonin receptors have also been shown to occur with age. Particularly, humans studied by positron emission tomography have shown that S2 serotonin receptors in the caudate nucleus, putamen, and frontal cerebral cortex decline with age (Wong *et al.* 1984). Regarding the levels of cholinergic receptors, however, the effects of aging are still unclear. Most studies seem to agree that there is a decrease in muscarinic binding in rodent aging brain, but there is controversy as to which regions show a significant reduction in receptor density (James and Kanungo 1976;Freund 1980;Morin and Wasterlain 1980;Lippa *et al.* 1981;Pedigo, Jr. *et al.* 1984). Taken together, these data point to disturbances in both neurotransmitters and neurotransmitter receptors occurring in the aging brain.

Increases in inflammatory signaling within the aging brain

Increased levels of inflammatory signaling are necessary for maintaining the function of all tissues, including the brain. However, in aging the brain appears to undergo at least three negative perturbations in inflammatory signaling and immune function. The first of these negative alterations is the presence of a chronic elevation in the levels of inflammatory signaling. Increases in multiple aspects of inflammatory signaling have been reported with aging including increased levels of tumor necrosis factor (TNF)-α, interleukin (IL)-1, and IL-6 (Spulber and Schultzberg 2010;Terao *et al.* 2002;Tha *et al.* 2000;Ye and Johnson

1999). Furthermore, studies have linked increases in each of these factors to the development of neuropathology and neuronal dysfunction in the aging brain (Griffin *et al.* 1995;Patterson 1995;Strauss *et al.* 1992). Additionally, the levels of cyclooxygenase and lipoxygenase, and their corresponding prostanoids and eicosanoids are known to be chronically increased during brain aging (Leone *et al.* 2007;Manev *et al.* 2000;Qu *et al.* 2000;Uz *et al.* 1998).

In addition to having a sustained increase in the basal levels of inflammatory signaling, aging is also known to impair the coordinated nature of the immune response (Desai *et al.* 2010;Giunta 2008). In this model, multiple aspects of an immune response (time required to mount a response, the extent to which the response is activated, and the rapidity to which the response is downregulated following the triggering event) are adversely affected by age. This promotes a more inefficient and ineffective inflammatory signaling within aging tissues such as the brain. Lastly, aging appears to alter the magnitude of peripheral immune cell infiltration into the brain following injury (Bolton and Perry 1998). Presumably, these cells contribute to the modulation of resident immune signaling within the aging brain, although the potential role of this observation to age-related brain inflammation remains to be fully elucidated.

Increases in oxidative stress within the aging brain

Oxidative stress occurs when the levels of oxidative damage reach a point that they promote the development of cellular and/or tissue dysfunction (Ding *et al.* 2006;Calabrese *et al.* 2010). An increase in oxidative damage to proteins, lipids, nucleic acids, and sugars in the aging and AD brain is well documented (Adelman *et al.* 1988;Berlett and Stadtman 1997;Cai *et al.* 1996;Finkel and Holbrook 2000;Gabbita *et al.* 1998;Good *et al.* 1996;Nunomura *et al.* 1999;Perry *et al.* 1998;Sayre *et al.* 1997;Smith *et al.* 1996;Sohal *et al.* 1995;Stadtman and Levine 2000;Stadtman and Oliver 1991). Furthermore, studies have demonstrated that each of these forms of oxidative damage is sufficient to result in decreased function of essential proteins and organelles, and thereby contributing to the development of brain aging. Studies on the levels and activity of antioxidants and antioxidant enzymes in the aging and AD brain have demonstrated a mixed bag of results (Calabrese *et al.* 2000;Calabrese *et al.* 2003;Calabrese *et al.* 2004;Calabrese *et al.* 2006;Droge and Schipper 2007;Kitani *et al.* 2001;Maier and Chan 2002;Massaad *et al.* 2009;Navarro and Boveris 2008;Schmitt-Schillig *et al.* 2005) and it remains unclear to what extent decreased levels of antioxidants may drive age-related increases in oxidative stress in the brain. Perhaps most importantly for the purposes of this review, the oxidative stress has been implicated in mediating the effects of neurotransmitter dysregulation and increased inflammatory signaling within the aging brain. Together, these data highlight a model for interplay between each of these cellular processes and the modulation of brain aging.

Structural changes in the aging brain

In the context of brain aging the best studied structural changes include synaptic changes, white matter changes, and vascular changes. Each of these changes is outlined below, and then later in the review is discussed in the context of aging and metabolic perturbations below.

Synaptic changes

Studies have documented an aging-related decrease in synaptic number occurring in specific domains within both experimental animal studies as well as studies of human brains (Bertoni-Freddari *et al.* 2006). However, the size of these synapses has been found to be increased in these experimental settings (Bertoni-Freddari *et al.* 1996;Bertoni-Freddari *et al.*

1992;Bertoni-Freddari *et al.* 1990). In both normal aging and AD brains, a negative correlation has been found between synapse number and synapse size. This appears to potentially be a compensatory response to minimize the effects of decreased synapse number, specifically to attempt to maintain the flux of information at the junctional zones, and to stabilize the synaptic contact per unit area (Scheff *et al.* 1990). However, ultimately the ability of the cortex to compensate seems to be exceeded and promote a decline in function (DeKosky and Scheff 1990).

The mechanisms responsible for synaptic changes during aging and AD are not clearly established. However, it has been demonstrated that oxidative stress may contribute to the pathophysiology of aging. However, the contribution of oxidative stress to the regulation of synaptic function is clearly complex. For example, it has been shown that superoxide is necessary for synaptic plasticity and memory in young animals (Klann *et al.* 1998;Klann 1998;Knapp and Klann 2002;Thiels and Klann 2002;Thiels *et al.* 2000), while chronically elevated levels of superoxide likely contribute to synaptic dysfunction during aging (Hu *et al.* 2006).

White matter changes

Through the use of neuroimaging technologies considerable advances have been made in our understanding of how white matter is altered in the aging brain. For example, regional differences in regards to age-related susceptibilities in white matter loss are known to occur (Guttmann *et al.* 1998;Hsu *et al.* 2008;Kennedy and Raz 2009;Lee *et al.* 2009), with prefrontal white matter observed to be most sensitive to the effects of aging (Gunning-Dixon *et al.* 2009). In addition to changes in white matter density, it is known that aging is associated with an increase in white matter lesions (Adami *et al.* 2008;Barber *et al.* 1999;Bugalho *et al.* 2007;Launer 2003;Roman 2004). These deleterious perturbations in connectivity throughout the brain are presumed to contribute to impairments in brain function. Despite our progress in being able to detect and measure white matter changes, there are two questions that need to be answered in this research area. Firstly, the role of white matter structural alterations as mediators of cognitive disturbances in the aging brain remain to be clarified beyond the point of correlation studies. Secondly, the mediators of white matter changes remain to be elucidated, although a role for metabolic disturbances as mediators of white matter pathology is clearly emerging.

Vascular changes

Aging, as well as many neurodegenerative disorders, are associated with structural and functional alterations of the cerebral vascularization (Aguero-Torres *et al.* 2006;Behrendt and Ganz 2002). Aging is characterized by a loss of elongation in endothelial cells, decreased number of endothelial mitochondria, and progressive impairment in endothelium-dependent vasodilation (Brandes *et al.* 2005;d'Alessio 2004;Finch 2005). Additionally, aging is associated with cerebral blood flow dysregulation and hypoperfusion, abnormal angiogenesis and remodeling, all of which may promote neuronal injury and neuron death (de la Torre 2004;Xiao *et al.* 2004). It is thought that an augmented production of pro-inflammatory cytokines and vasoactive molecules could be the responsible of the cognitive decline, potentially through a mechanism of suppression of cerebral blood flow and amplification of cellular stress (Zlokovic 2005).

Another feature of senescent endothelial cells is the increased generation of endothelial adhesion molecules (d'Alessio 2004), markers of endothelial inflammation. Increased levels of blood adhesion molecules have been reported in several brain disorders, namely atherosclerosis, ischemic stroke, cerebrovascular disease and AD (Fassbender *et al.* 1999;Frohman *et al.* 1991;Roher *et al.* 2004). In addition, soluble intracellular adhesion

molecule-1 (sICAM-1) has been shown to be present in high levels in cerebrospinal fluid of individuals with inflammatory diseases of the central nervous system, and it has been suggested that cerebral endothelial cells are the primary source of sICAM-1 (Roher *et al.* 2004). This raises the possibility for molecules such as sICAM-1 contributing to vascular reactivity in the aging brain.

An increase in blood brain barrier (BBB) permeability has been documented to occur during aging in healthy individuals. Morphological changes of BBB have been also shown in rodent models of aging (Hosokawa and Ueno 1999). Since some of these models exhibit increased oxidative stress at an early age (Yasui *et al.* 2003) prior to the development of other pathological features, it has been suggested that alterations in BBB could be promoted via oxidative stress-mediated mechanisms. On the other hand, it has been demonstrated that hypertension, a common feature of older people, can induce BBB alterations (Nag and Kilty 1997;Baumbach and Heistad 1988). Taken together, these findings highlight the complexity in understanding the relationship between oxidative stress and morbidities such as hypertension, in regulating the biological aging of the brain.

Variability in rates and extent of brain aging

While it is clear that chronological aging promotes a generalized aging phenotype in the brain, it is equally clear that there is dramatic and significant variability in both the rate and severity of such alterations. For example, studies in humans document that there is considerable variability in regards to deterioration in cognitive performance with advancing age (Williams *et al.* 2005;Hultsch *et al.* 2002). Since variability at the performance level could be reflecting variations and alterations at a cellular and system level in the brain, understanding the basis for this observation is likely important to understanding the basis of brain aging, and developing interventions for promoting successful brain aging.

Our laboratory, as well as numerous other laboratories, believes there is an important role for age-related metabolic perturbations in mediating not only brain aging, but also in explaining the basis for the variability in the rates of brain aging. There is mounting evidence for metabolic dysfunction, in particular conditions such as obesity and insulin resistance, as significant contributors to the aging of modern westernized societies.

It is well known that aging is associated with the progressive development of generalized insulin resistance (DeFronzo 1981;Elahi *et al.* 2002), inhibition of lipolysis (Kumar *et al.* 1999;Miller and Allen 1973;Nyberg *et al.* 1976) and a loss in hepatic control of glucose production (Gupta *et al.* 2000) and triglyceride secretion (Bravo *et al.* 1996). Cumulatively, each of these manifestations is sufficient to promote an increase in a number of morbidity factors including cardiovascular and cerebrovascular diseases, gastrointestinal and respiratory alterations, cancer, and cognitive decline and dementia (Haslam and James 2005;Perlmuter *et al.* 1988;Qiu *et al.* 2007). Moreover, people from countries with traditionally higher mean lifespan are known to undergo an increase in a number of morbidities after changing their nutritional intake towards energy-rich diets. However, the availability of pharmacological treatments for these morbidities has allowed for these deleterious morbidities to not significantly decrease lifespan in the population (Picard and Guarante, 2005). Despite such progress, it remains unclear whether pharmacological management of metabolic disorders (obesity, insulin resistance, etc.) is able to also preserve brain function as these same individuals age.

Age-related neurologic manifestations include sensory deficits (taste, smell, vibration, vision, and hearing), disturbances in sensing pain, motor dysfunction (altered gait and posture), sleep disturbances, and impaired memory and cognition. For example, aging promotes the slowing of central processing and therefore may prolong the time it takes to

complete tasks. Declines in motor strength, reflex responses, and reaction time with aging are related to sensori-motor changes. Changes associated with aging also include mild forgetfulness, a decrease in vocabulary, and learning difficulties (Braun and Anderson 2006). These changes typically occur by the seventh decade of life, but have a great deal of heterogeneity and variability in regards to the severity of dysfunction which is observed in elderly individuals (McClearn 1997). While the basis for the variability in brain aging is not known, one possible mediator is metabolic dysfunction, with increased levels of dietary fat intake serving as a potential mediator of metabolic dysfunction. For example, high-fat diets are known to be sufficient to promote insulin resistance and obesity in both humans and rodents (Buettner *et al.* 2007;Damjanovic and Barton 2008;Oakes *et al.* 1997;Tschop and Heiman 2001). What is less known is what effect high-fat diets have on aging, particularly brain aging. With the intersection of an increasing aging and obese society, that increasingly regularly consumes a high fat diet, it is clear that understanding the impact of diet-induced metabolic perturbations on the aging brain is of mounting clinical importance. The possible contribution of metabolic dysfunction as a modulator of brain aging raises the possibility that factors such as diet may be centrally linked to the regulation of brain aging. In particular, diet-induced metabolic dysfunction likely serves as a pro-aging stimulus for multiple aspects of brain biochemistry and physiology. Interestingly, several clinical and epidemiological studies, as well as experimental evidence in rodents, suggest that the presence of Western diet-induced metabolic dysfunction is sufficient to promote cognitive decline and even dementia, thus accelerating the normal process of aging.

Several abnormalities of carbohydrate and lipid metabolism have been commonly observed to increase in Western societies with age, namely insulin resistance, hyperglycemia, hyperinsulinemia, dyslipemia, triglyceridemia, and free fatty acid alterations (Astrup *et al.* 2008;Bullo *et al.* 2007;Matia *et al.* 2007;Pasinetti and Eberstein 2008;Steemburgo *et al.* 2007). However, it is not yet completely understood whether these alterations become manifest as a consequence of the molecular mechanisms operating in the aging process or as a result of the influence of many cultural/environmental factors such as diet and a decrease in physical activity (Paolisso *et al.* 1995).

In the context of brain aging metabolic dysfunction must be understood not only in terms of diabetes but also in terms of pre-diabetic states where individuals exhibit hyperinsulemia but remain euglycemic. A high concentration of circulating insulin (hyperinsulinemia) may represent a failure in insulin metabolism as well as a compensatory response to insulin resistance. In either case, hyperinsulinemia is correlated with insulin resistance in pre-diabetic individuals (Howard *et al.* 1998;Laakso 1993). At this point it is worth to mention that many studies have reported that the elderly are more insulin resistant that young individuals (Chen *et al.* 1985;Coon *et al.* 1992;DeFronzo 1979;Ferrannini *et al.* 1996;O'Shaughnessy *et al.* 1992;Rowe *et al.* 1983), although this point remains controversial (Ahren and Pacini 1998;Boden *et al.* 1993;Broughton *et al.* 1991;Dechenes *et al.* 1998;Pacini *et al.* 1988). Important to take into account is that several factors may influence insulin action and secretion, including the degree and type of obesity (Peiris *et al.* 1986), level of fitness (Kirwan *et al.* 1993;Miller *et al.* 1994), and circulation hormone profiles (Nielsen *et al.* 1997;Rizza *et al.* 1982a;Rizza *et al.* 1982b). Additionally, some studies have shown that central obesity (increased waist-to-hip ratio) is associated to insulin resistance and aging. Furthermore, the intra-abdominal fat depot in central-obesity has been postulated to contribute most to the development of insulin resistance, and therefore the insulin resistance observed in aging may be related more to changes in body composition during aging than to aging *per se*. Moreover, intra-abdominal fat has been postulated to be the most metabolically active of the adipose depots and correlates with insulin resistance and age in healthy nondiabetic individuals regardless of gender and after controlling for obesity (Cefalu 2001;Cefalu *et al.* 1995).

Adiposity

Adipose tissue has long been considered as a mere energy-store but is increasingly appreciated for its roles in participating in several physiological events such as inflammation, angiogenesis, hypertension, and vascular homeostasis (Fruhbeck 2008). Moreover, the adipose tissue synthesizes and secretes a large number of factors collectively termed “adipokines” (Fruhbeck 2008). More than 50 different adipokines have been identified and characterized for their role in influencing energy homeostasis and feeding behaviour (Ahima and Osei 2008). However, an increasing number of studies have identified that adipokines may play a role in mediating long-term potentiation, neuroprotection, and neuroinflammation.

A major role for adipose tissue (adipocytes) is to sequester and store circulating lipid, which protects other cells and tissues in the body form the cytotoxic effects of free fatty acids in the circulation. Failure of adipocytes to effectively remove free fatty acids from the circulation is believed to contribute to a variety of health complications including hypertension, atherosclerosis, and ultimately the development of metabolic syndrome (Fagot-Campagna *et al.* 1998;Moller and Kaufman 2005;Smith and Wilson 2006;Wang *et al.* 2008). Conversely, the deposition of adipose/lipid into muscle, liver, or bone marrow is known to promote not only metabolic syndrome but localized tissue dysfunction (Kuk *et al.* 2009). Therefore, it is clear that adipocytes perform essential functions for the overall well being of individuals, but it is equally clear that adipose in the incorrect places or in excessive quantity also negatively impacts the health of an individual.

Aging is known to impair the ability of adipocytes to sequester free fatty acids, and promote the release of pro-inflammatory signals from adipose tissue. Many studies have suggested that the decline in specific adipose depots is due to a decrease in adipocyte size and not a reduction in number. Additional studies have demonstrated that aging impairs the process of adipocyte differentiation resulting in an increase in more highly reactive preadipocytes. Preadipocytes do not have the capacity to sequester free fatty acids from the circulation to the same degree as mature adipocytes, and an age-related increase in preadipocytes may therefore result in promotion of adverse events in regards to the regulation of circulating lipids. Taken together, these studies strongly suggest that aging has direct and complex effects on adipose tissue including a redistribution of adipose depots as well as fundamental alterations in the cell biology of adipocytes, which together may promote metabolic dysfunction and inflammatory signaling throughout the body.

An increase in visceral adiposity is a common feature of aging, and epidemiological evidence supports its role as a prominent risk factor for insulin resistance, diabetes, and mortality from atherosclerotic cardiovascular disease (Ferrannini *et al.* 1997;Fujimoto *et al.* 1999;Lamarche 1998;Shimokata *et al.* 1989;Cefalu *et al.* 1995). Typically, elderly people have a lighter body weight as compared to younger individuals but increased waist circumference, consistent with elevated levels of abdominal adipose tissue. It has been observed that a complex relationship exists between aging, obesity and increased visceral fat which is not always sufficient to promote insulin resistance (Carr *et al.* 2004). It has been reported that caloric restriction extends life in a variety of species and decreases the development of most age-related diseases, and it is believed that these effects may be due to the ability of dietary restriction to reduce fat stores, especially visceral fat. In addition, the removal of visceral fat in rats has demonstrated to improve insulin action, delay the onset of age-dependent insulin resistance, glucose intolerance and diabetes, as well as increase in mean and maximum lifespan in rodent models of obesity and diabetes (Barzilai *et al.* 1999;Gabriely *et al.* 2002). Visceral fat removal has shown to improve metabolism even without any changes in body weight, fat mass, and lean body mass (Gabriely *et al.* 2002). It

is thought that surgical removal of visceral fat depots disrupts a cross-talk between fat depots and multiple sites within the body (Wang *et al.* 1999).

The issue of adiposity itself in aging is a complex biological problem to study. For example, total fat mass is known to peak at middle age in both humans and rodents, which is followed by a precipitous decline with advancing age. However, the decline in fat mass with age does not coincide with a decrease in percent body fat because lean muscle mass is also decreased with age. Therefore, body mass index and other such measures do not do an accurate identification of the dramatic increase in ectopic fat and visceral fat deposition that occurs in aging. Additionally, it is poorly understood how such changes in adiposity contribute to the development of chronic disease in the elderly, or the development of metabolic syndrome which occurs in 40-70% of the elderly.

Impact of high-fat diets on aspects of aging

High-fat diets (HFD) have been used for many years to study the effects of increased adiposity, dyslipidemia and insulin resistance in rodents. It has been shown that the disturbances originated by high-fat feeding closely resemble the metabolic disturbances observed in humans (Woods *et al.* 2003). Several different types of HFDs are commonly utilized in the study of diet-induced obesity and insulin resistance. One problem with this literature is that all of the effects of these various HFDs (which vary in the amount and source of dietary fat) have all been summarized as being “HFD effects”. This has inevitably been source of great variability in the findings reported. Additionally, many studies have contrasted the effects of HFD to animals fed a standard chow diet, which dramatically affects the interpretation of findings as compared to using appropriate low fat control diets. This is because standard chow diets differ in the amount and source of dietary fat, as well as other dietary components, and therefore do not allow controlled studies on the specific effect elevated dietary fat has on individual parameters.

Despite the tremendous progress which has been made in our understanding of dietary fat and obesity/diabetes with using these different HFDs, it is important to point out that relatively little is currently available in regards to the study of HFDs and brain aging. For example, studies have not firmly established the ability of HFDs to promote or accelerate different aspects of brain aging. Additionally, studies have not examined in a comprehensive manner what specific aspects of perturbed metabolism (high fasting glucose, hyperinsulemia, elevated adiposity, cholesterol level, fatty acid levels, etc.) may be most involved in the promotion of brain aging.

In addition to the use of diets, many rodent strains have been utilized as models of obesity, and the use of these models has contributed strongly to the understanding of obesity (Kanoski *et al.* 2007;Wu *et al.* 2004). In particular, the ob/ob mouse, which is characterized by an increase in both number and size of adipocytes, and also by its perturbations in leptin treatment, has been used to test the effects of obesity on the brain (Itateyama *et al.* 2003;Terao *et al.* 2008). However, due to the polygenic character of this disorder and the numerous congenic perturbations observed in these rodent models (ob/ob mice, fa/fa Zucker rats) they have an obvious limitation in the study of brain aging. Thus, HFD-induced models of metabolic dysfunction should be considered the best option for studying the effects of metabolic dysfunction on human brain aging.

HFD can accelerate age-related adiposity

As pointed out above, aging leads to a redistribution of body fat, with a stabilization or enhancement of visceral fat and fat deposition into tissues such as liver, muscle, and bone. Similarly, HFD consumption has been also found to increase visceral fat mass (Park *et al.*

2001). This increased amount of visceral adipose tissue usually results in elevated concentrations and flux of circulating free fatty acids into the portal circulation (Bjorntorp 1990), since the abdominal fat has a high lipolytic activity and is very sensitive to adrenergic stimulation due to the peculiarities of the lipolytic cascade (Wahrenberg *et al.* 1989). This elevation of circulating free fatty acids is associated with increased hepatic glucose production (Ferrannini *et al.* 1983), reduced hepatic insulin clearance (Svedberg *et al.* 1990), decreased peripheral glucose uptake (Ferrannini *et al.* 1983), and increased very-low-density lipoprotein-triglyceride synthesis (Kissebah *et al.* 1976). Thus a higher rate of lipolysis is able to cause the disturbances in glucose and lipoprotein metabolism associated with diet-induced obesity. HFD consumption is therefore capable of promoting novel metabolic perturbations as well as accelerate individual aspects of age-related metabolic disturbances.

HFD can exacerbate peripheral inflammation

HFD-induced metabolic dysfunction has been shown to positively correlate with markers of acute-phase response such as C-reactive protein (CRP) (Koenig *et al.* 1999;Mendall *et al.* 1996) and fibrinogen (Juhan-Vague *et al.* 1993). Elevated levels of CRP have been associated with high fasting glucose, high serum lipids, high body mass index (Koenig *et al.* 1999;Mendall *et al.* 1996;Yudkin *et al.* 1999) . It has been shown that chronic, subclinical inflammation is part of insulin resistance syndrome and that dyslipidemia, abdominal obesity, low insulin sensitivity and hypertension parallel increasing levels of CRP (Festa *et al.* 2000). It is possible that HFD consumption can provoke cytokine secretion to the point it leads to insulin resistance, and may thereby accelerate age-related processes leading to insulin resistance (Festa *et al.* 2000).

Decreased insulin sensitivity may be responsible of the increased CRP expression, since the physiological effect of insulin on hepatic protein synthesis includes the stimulation of albumin synthesis and inhibition of fibrinogen synthesis (De Feo *et al.* 1993). Resistance to insulin would then be expected to lead to increased synthesis of acute-phase proteins, such as fibrinogen and CRP. In addition to these mechanisms, HFD via the acceleration of adipose reactivity may promote a generalized increase in inflammatory signaling as the result of adipose-derived adipokine signaling throughout the body. All these data indicate that subclinical inflammation would be expected to be present early in HFD-induced metabolic dysfunction (such as elevated adiposity and insulin resistance), and thereby link HFD-induced modulation of metabolic dysfunction to age-related changes in inflammatory signaling.

Molecular pathways for HFD effects on metabolic dysfunction

Mitochondrial dysfunction—Several studies have related diet-induced metabolic disturbances with mitochondrial alterations. For example, a decreased expression of genes involved in mitochondria biogenesis has been observed following HFD consumption (Handschin and Spiegelman 2006;Nisoli *et al.* 2007;Shen *et al.* 2004). Similarly, HFDs have been demonstrated to decrease the levels of mitochondrial complex 1 activity (Nisoli *et al.* 2007). Complex I, also known as NADH-ubiquinone oxidoreductase, is a membrane enzyme complex of the mitochondrial electron transport chain that catalyzes electron transfer from NADH to ubiquinone thus generating proton motive force. Decreased levels of this complex will have pronounced deleterious effects on mitochondrial energy-generating efficiency, which together with an altered biogenesis, would be expected to compromise energy availability in the aging brain. HFD effects on mitochondria may therefore serve as a potential mechanism by which metabolic dysfunction induces by HFD consumption modulates the rates of brain aging.

Oxidative stress—Oxidative stress is thought to be one of the earliest steps in HFD-induced pathogenesis (Matsuzawa-Nagata *et al.* 2008). Reactive oxygen species (ROS) are normal byproducts of biological processes but are known to be capable of reactivity with proteins, nucleic acids, and lipids. Mitochondrial-derived ROS are believed to be a major site of HFD-induced oxidative stress (Cecarini *et al.* 2007;Lau *et al.* 2007;Joseph *et al.* 2005), although studies have also identified a role for NADPH oxidase in HFD induced oxidative stress (Bruce-Keller *et al.* 2010). Increased levels of oxidative stress have been found in animals and humans following HFD-induced metabolic dysfunction (Matsuzawa-Nagata *et al.* 2008;Iqbal 2007;Yaffe 2007;Moreira *et al.* 2008;Furukawa *et al.* 2004;Urakawa *et al.* 2003;Diniz *et al.* 2006;Fridlyand and Philipson 2006;Mantena *et al.* 2008). Taken together, these data suggest that the HFD consumption may play an important role in regulating age-related increases in oxidative stress.

Sirtuin signaling—Sirtuins are a family of NAD^+-dependent histone/protein deacetylases involved in a broad range of physiological functions, including control of gene expression, metabolism, and aging (Bordone and Guarente 2005). Many studies have associated sirtuins with caloric restriction-mediated health benefits including increased longevity (Blander and Guarente 2004;Gray and Ekstrom 2001;Smith *et al.* 2000;Tanner *et al.* 2000). Because of the ability of caloric restriction to promote beneficial effects on metabolism and brain aging, these studies identify a potentially important role for sirtuins in promoting the beneficial effects of caloric restriction on the brain. Seven distinct sirtuins (Sirt1-Sirt7) have been described in mammals, being Sirt1 expressed in several tissues and implicated in effects such as stress resistance, reduced apoptosis, and metabolic changes associated with calorie restriction (Blander and Guarente 2004).

Almost all Sirt1-deficient animals die during early postnatal development (Chen *et al.* 2005), with reduced triglycerides, insulin, and blood glucose observed in these same animals. Such findings further link Sirt1 to metabolic regulation. Sirt1 is also present in white adipose tissue, where has been shown to reduce adipogenesis and triglyceride accumulation in the lipid droplets of a cell model of white adipocytes. These observations have been related to decreased expression of genes involved in fatty acid metabolism, such as peroxisome proliferator-activated receptors gamma (PPARγ). Additionally, *in vivo*, fasting induces Sirt1 and promotes lipolysis by inhibiting PPARγ-mediated fatty acid trapping. The function of Sirt1 in the release of insulin by pancreatic β cells has also been studied, and it has been found that reduction of Sirt1 expression in β cell lines promotes a reduction in insulin secretion (Bordone *et al.* 2006).

Studies have shown that a modest overexpression of Sirt1 protects hepatic lipid and glucose metabolism from damage caused by HFDs. Additionally, Sirt1 has been found to be involved in the protection from metabolic syndrome. Sirt1 activators have been found to be beneficial for mitochondrial and metabolic function in obese rodents and are currently being studied as potential treatments for type-2 diabetes (Milne *et al.* 2007). It has been reported that moderate Sirt1 overexpression in mice prevents HFD-induced glucose intolerance and nonalcoholic fatty liver disease (Pfluger *et al.* 2008). Together, these data raise the possibility of HFDs mediating their effects on the aging brain in a sirtuin-dependent manner, although more work in this area is clearly needed.

Evidence for HFD exacerbating brain aging

HFD consumption is thought to induce changes not only in energy metabolism but also in brain function. Considerable clinical evidence suggests that HFD consumption and the presence of metabolic dysfunction are sufficient to exacerbate brain aging, promoting the development of cognitive alterations including dementia (Yaffe 2007;Haan *et al.*

2003;Taylor and MacQueen 2007). Moreover, obese adults have shown more severe brain atrophy than non-obese adults (Ward *et al.* 2005), further linking HFD consumption to brain perturbations.

Insulin has been suggested to play important roles in regulating memory, so any disturbance in insulin signaling would be expected to have a negative impact on memory (Luchsinger *et al.* 2004). Some studies have demonstrated that HFDs are able to increase amyloid beta peptide (Aβ) levels and Aβ-neuropathy in brains of mice exhibiting Alzheimer's disease (AD) pathology (Ho *et al.* 2004). Experimental evidence suggests that alterations in insulin metabolism may influence the onset of AD through their influence on the synthesis and degradation of Aβ peptides. Moreover, high levels of circulating insulin may also promote the accumulation of Aβ peptides by directly competing with Aβ for the insulin-degrading enzyme (IDE), thereby limiting Aβ degradation by IDE. However, whether the risk of AD is increased in human patients with diabetes mellitus is a matter of some debate. Some studies have reported that diabetic patients have elevated risk of developing AD (Leibson *et al.* 1997;Ott *et al.* 1999;Arvanitakis *et al.* 2004;Craft *et al.* 1998). However, several clinical studies have indicated that diabetes does not seem to be associated to AD (Luchsinger *et al.* 2004;Tariot *et al.* 1999;Curb *et al.* 1999;MacKnight *et al.* 2002;Akomolafe *et al.* 2006). Moreover, almost all neuropathological studies so far have failed to detect any associations between AD-related pathology and diabetes (Heitner and Dickson 1997;Petrovitch *et al.* 2000;Peila *et al.* 2002;Arvanitakis *et al.* 2006;Janson *et al.* 2004). Instead, diabetes has been associated to the presence of cerebral infarcts (Peila *et al.* 2002;Arvanitakis *et al.* 2006). Since diabetes present altered capillary blood vessels in the peripheral vasculature, it is not surprising that diabetes promotes changes in brain microvasculature. Interestingly, data from the Framingham study has demonstrated a link between type-2 diabetes and lower cognition scores (Elias *et al.* 1997), and hyperglycemia has been found to negatively influence cognitive impairment in population-based studies (Franceschi *et al.* 1984;Langan *et al.* 1991;Messier *et al.* 1999;Robertson-Tchabo *et al.* 1986).

Another metabolic disturbance associated with HFD-consumption and obesity is hypertension which is considered a great risk factor for cerebral stroke (Rosamond *et al.* 2008). One possible mechanism by which obesity may increase the risk of stroke is via an alteration in cerebral perfusion. Cerebral perfusion is regulated through active constrictor and dilator mechanisms and by the physical properties of the cerebral vasculature, such as myogenic tone and vessel structure. Increased myogenic tone has been reported to occur in middle and posterior cerebral arteries from spontaneously hypertensive rats, as well as vasopressin-deficient rat (Dunn *et al.* 1998;Gonzalez *et al.* 2008). Additionally, a great body of evidence has reported vascular remodeling in the cerebral circulation in different models of hypertension, spontaneously hypertensive rats among them (Dunn *et al.* 1998;Arribas *et al.* 1996;Baumbach and Heistad 1989). The most common changes in hypertensive populations are mechanical and architectural properties of the cerebral vasculature, particularly an inward remodeling of the large arteries (Baumbach *et al.* 1988;Baumbach and Heistad 1989;Baumbach and Heistad 1988). Inward remodeling not only increases the risk of flow obstruction but it is also detrimental in ischemic conditions. After ischemia, brain vessels are near-maximally vasodilated, so reductions in maximum lumen diameter become a constraint on perfusion. In addition, it is well known that alterations of arterial pressure cause deleterious changes in vascular structure, as vessels become rigid, wall thickness can increase and lumen diameter can decrease (Baumbach and Heistad 1989;Heistad *et al.* 1990), causing an extra impairment of blood flow during ischemia. In addition, studies carried out in adult obese Zucker rats (OZRs) with moderate hypertension and severe insulin resistance have demonstrated an increased cerebral vascular myogenic tone, inward cerebral vascular remodeling, and increased cerebral tissue death after ischemia/reperfusion injury in these rodents (Osmond *et al.* 2009). Important to note, young

OZRs, which are obese and insulin resistant but not yet hypertensive, did not show any of those deficits (Osmond *et al.* 2009). Additionally, other studies carried out in leptin deficient ob/ob mice and also in diet-induced obese mice have shown that obesity worsens the response to ischemia (Nagai *et al.* 2007;Terao *et al.* 2008). All these data together suggest that obesity together with prolonged moderate hypertension serve as risk factors for cerebral vascular dysfunction and stroke.

Dyslipidemia is another common disease associated with HFD consumption. More than 50% of the US population older than 20 years old have cholesterol levels of 200 mg/dl or higher, and more than 18% have levels of 240 mg/dl or higher. The link between dyslipidemia and having a higher risk of cognitive impairment or dementia is controversial (Kuo *et al.* 1998;Wieringa *et al.* 1997;Lesser *et al.* 2001;Scacchi *et al.* 1998). Reduced levels of high-density lipoprotein (HDL) cholesterol have been reported in some cases of dementia (Kuo *et al.* 1998;Wieringa *et al.* 1997;Muckle and Roy 1985;Kuriyama *et al.* 1994;Kuriyama *et al.* 1992;Michikawa 2003;van Exel *et al.* 2002) but not all cases of dementia.

Direct evidence for HFD promoting brain pathogenesis

A large body of evidence from rodent and human studies has demonstrated that HFD-induced metabolic dysfunction promotes cognitive alterations and dementia (Craft 2005;Kumari *et al.* 2000;Li *et al.* 2007;Pasinetti *et al.* 2007;Razay *et al.* 2007). Different studies have been performed on rats in order to clarify the influence specific diets may have on different aspects of cognition. Interestingly, it has been documented that even maternal HFD consumption sensitizes offspring to the deleterious consequences of HFD (White *et al.* 2009). Studies carried out in rats have shown that, in agreement with biochemical and physiological evidence, a diet high in saturated fatty acids can impair learning and memory functions (Greenwood and Winocur 1990;Granholm *et al.* 2008). Moreover, direct injection of triglycerides into the brain has shown to have detrimental consequences for learning and memory (Farr *et al.* 2008). In addition, the strong relationship between obesity and cognitive impairment found in animals (White *et al.* 2009;Granholm *et al.* 2008;Baran *et al.* 2005;Winocur and Greenwood 2005) supporting an association between obesity and deficits in learning, memory, and executive functioning in human patients (Elias *et al.* 2003;Elias *et al.* 2005). At present, oxidative stress and brain inflammation are thought to play key roles in HFD-induced cognitive loss, since brain markers of oxidative stress and inflammation have been found to be increased in mice fed HFD which show clear cognitive impairment (Pistell *et al.* 2010;Souza *et al.* 2007;Zhang *et al.* 2005). Furthermore, HFD consumption has been shown to increase age-related oxidative stress in the brain (Mattson *et al.* 2003;Perry *et al.* 2003). For example, rodents fed high-fat or high-calorie diets have shown to have increased levels of oxidative stress (Zhang *et al.* 2005) and protein oxidation (Souza *et al.* 2007) in the brain. However, it is still unclear whether oxidative stress in HFD models of obesity is the result of obesity *per se*, or is more related to the associated metabolic dysfunction. Although there is a clear relation between obesity and brain inflammation, the real mechanisms whereby HFD contributes to brain inflammation and cognitive impairment also remain elusive. Certainly, brain function is sensitive to inflammatory pathways and mediators. For example, IL-1β and IL-6 are able to alter physiologic mechanisms involved in cognition and memory (Bellinger *et al.* 1995;Jankowsky and Patterson 1999;Gemma and Bickford 2007). Adiponectin and leptin, two well known adipokines, could be considered as important links between obesity, insulin resistance and related inflammatory disorders (Antuna-Puente *et al.* 2008;Fantuzzi 2005). Adiponectin has been shown to exhibit neuroprotective and anti-inflammatory properties in the brain (Chen *et al.* 2009) and to have important roles against the development of insulin resistance, dyslipidemia and atherosclerosis (Rasouli and Kern 2008). Leptin has also been reported to have important

roles in cognition (Harvey *et al.* 2005;Oomura *et al.* 2006) and in the modulation of inflammatory signaling in microglia (Pinteaux *et al.* 2007). Among the afferent inputs that the brain uses to adjust food intake and energy metabolism, leptin is one of the best understood, supressing food intake and increases energy expenditure (Friedman and Halaas 1998). Studies such as these raise the possibility of roles for leptin in the aging brain that are independent of leptin effects in the hypothalamus and the regulation of feeding behavior.

There is also reasonable evidence for believing that insulin might also play a role in mediating the effects of HFD consumption on the brain, since insulin is known to act within the hippocampus. *In vitro* studies have shown that insulin can modulate hippocampal synaptic plasticity (Izumi *et al.* 2003;van der Heide *et al.* 2005;Zhao *et al.* 2004). In addition, it is also known that hippocampal cognitive performance strongly depends on glucose supply (Gold 2005;McNay *et al.* 2000;McNay and Gold 2002), which is regulated in larger part by peripheral insulin levels. It has been reported that hippocampus of AD brains have lower levels of glucose utilization and a corresponding impairment in insulin signaling (Frolich *et al.* 1998;Hoyer 2004;Steen *et al.* 2005).

Summary

Considerable evidence suggests a role for metabolic dysfunction as a modulator of brain aging, and consequently raises the specter of stressors such as HFD consumption as mediators of accelerated brain aging. In this model HFD consumption promotes a myriad of metabolic disturbances during aging, which directly and/or indirectly modulate the rate the brain ages. Of particular interest is the possibility that metabolic dysfunction during aging (in response to HFD consumption, genetics, physical activity, etc.) accounts for the considerable variability in the rates of brain aging that are observed in the elderly. Despite the progress made in this research area, several key questions remain to be answered. For example, which component(s) of metabolic dysfunction are responsible for the initiation/propagation of brain aging? How do individual aspects of metabolic dysfunction mediate neurochemical, structural, and/or functional changes in the aging brain? Answering these questions will likely contribute to not only our understanding of brain aging, but also to the development of therapeutic interventions which promote healthy brain aging.

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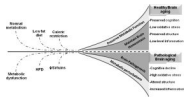

Figure 1. Interplay between metabolic dysfunction, high fat diets and brain aging

Consumption of a high fat diet (HFD) and the presence of metabolic dysfunction (insulin resistance, adiposity, etc.) are associated with pathological brain aging. Pathological brain aging is linked to excessive cognitive decline, high oxidative stress, alterations in brain structure, and increased inflammatory signaling. In contrast, consumption of a low fat diet, caloric restriction, and maintenance of metabolic function results in successful brain aging. The successful brain aging is defined as preserved cognition, decreased oxidative stress, preserved structure, and reduced inflammatory signaling.