Chapter 3

High-Fat and Cholesterol Intake Affects Brain Homeostasis and Could Accelerate the Development of Dementia: A Systemic View

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Additional information is available at the end of the chapter

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Abstract

Alzheimer's disease is the most common type of dementia in occidental countries. The majority of the cases develop the disease for no genetic reasons; therefore, it is crucial to establish which environmental factors trigger the development of the disease. It has been proposed that nutritional habits, especially main components of Western countries' diet such as saturated fat or cholesterol, increase the risk for development of Alzheimer's disease (AD) and/or accelerate the onset of the disease, which is a big concern in countries where obesity is a public health problem. It is crucial to understand the links between alimentary habits and the development of AD and other types of dementia. A possible mechanism is the disruption of blood–brain barrier (BBB), which is the protection of the brain from circulating blood. Such disruptions can result from consuming high-fat diet (HFD) or high-cholesterol diet (HCD) and inflammation produced by alteration in brain vasculature resulted for chronic consumption of such type of diets. What has named a "Systemic view" comprises the idea that; what happens outside of the brain environment does affect brain functioning and the modifications experienced in the brain environment resulted from the influence of external factors will affect the entire body. In the current chapter, we will review the state of the art in the studies of the impact of a diet rich in fat or cholesterol on the brain and how the alterations induced in other organs can impact brain functioning increasing the susceptibility of development of dementia.

Keywords: high-fat diet, high-cholesterol diet, Alzheimer's disease, blood–brain barrier, brain plasticity, cognition

1. Introduction

In the recent decades, the population in the industrialized Western countries has become remarkable sedentary and have had a considerable increase in the intake of what has been called "fast food," meals that are rich in fat and carbohydrates and contain elevate levels of cholesterol as well. The elevated consumption of fast food has had a strong impact on public health, which has important repercussions in several levels including an economic impact due to the elevated cost of a chronic use of specialized health services and a detrimental effect in both, life quality and expectancy for the patients. Among the adverse health effects of this type of diet, we can mention obesity, vascular diseases, and metabolic syndrome, and it has been recently proposed that it can increase the risk of developing Alzheimer's disease (AD), which is the most common type of dementia in elderly people. It is considered that a particular type of diet could accelerate the progress of the disease for a not yet well-known mechanism [1]. It is a revolutionary idea, since we have had for several years the conception that brain is actually protected by the blood–brain barrier (BBB); however, experimental evidence suggests that the consumption of diets rich in fat can disrupt the permeability of BBB, making it vulnerable to systemic molecules that could trigger degenerative processes [1, 2].

In the current chapter, we will review the state of the art related to the impact of diets rich in fat or cholesterol on the brain, and how the alterations induced in other organs can impact brain functioning and could increase the susceptibility to develop dementia. The bibliographic revision was carried out running an exhaustive search on the research articles related to the topic employing the database of the US National Library of Medicine, National Institutes of Health, PubMed.gov. Firstly, reviewing the most recent papers and those with the most relevant information. Thereafter, we carefully followed the references cited by the reviewed articles in order to study the grounding data on the subject and which direction it followed until our days in order to document the accuracy and evolution of the data.

2. Findings on amyloid-β production induced by saturated fat diet in noncerebral tissue

One of the histopathological hallmarks of AD is the extracellular deposition of amyloid-β peptide (Aβ) in the brain. It is widely accepted that Aβ deposition occurs when the neuronal synthesis of the peptide exceeds the clearance capacity [3, 4]. However, some decades ago, the idea was proposed that Aβ generated systemically could pass the BBB and be deposited in the brain, since Aβ was detected in noncerebral biological fluids. Such idea raised from grounding data of Seubert et al. [5], who demonstrated that Aβ fragment comprising the amino acids 13–28 can be detected in cerebrospinal fluid and plasma of several species including human as well as in conditioned media from human brain cell cultures. It originated the idea that cerebral Aβ deposits could be generated systemically and for unknown mechanism, accumulate in the brain where they affect the capacity, to be clear, increasing the amount of the peptide and eventually form the extracellular deposits. A good amount of data has focused on this idea

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since then. An interesting line of study has focus on the production of Aβ by noncerebral tissue induced by consumption of diets rich in fat. One of the physiological functions of Aβ is relate to lipids metabolism and many Aβ transport proteins have been associated with lipids *in vivo* [6]. The association of the Aβ soluble fraction with high-density lipoproteins from healthy human plasma and cerebrospinal fluid was reported as well [7, 8]. The association between lipids and Aβ was demonstrated in a very elegant study where Aβ activity was followed labeling it with radioactivity, and it was found that the peptide is expressed in tissues rich in fat, such as spleen, marrow, liver, adipose tissue, brain, kidney, lung, and skeletal muscle. It was shown that the expression of Aβ is associated with postprandial lipoproteins such as chylomicrons, lipoproteins that are in charge to move dietary fat from intestine to the target organs. These associations remain during lipolysis and tissue uptaking processes [9]. Therefore, it can be proposed that an increased plasmatic amount of such proteins containing Aβ could produce an imbalance and could even be delivered in brain contributing to cerebral amyloidosis, one of the responsible events related to Alzheimer's disease [9, 10]. The natural question is: how can we increase the amount of Aβ associated to postprandial lipids? One answer is the intake of diets rich in fat or cholesterol because they could break the balance of lipids content, but by which way? An interesting direction has been to study the expression of Aβ in organs rich in lipids and if such expression is regulated by fat or cholesterol diets.

Koudinov et al. [11] reported that hepatocytes secrete amyloid-β as a lipoprotein complex. Another organ where it has been documented that Aβ is produced is the small intestine. Given the evidence that Aβ is associated to postprandial lipoproteins, chylomicrons, Galloway et al. [10] followed this line of evidence and studied small intestinal epithelial cells (where the chylomicrons are produced). They fed wild-type mice with low- or high-fat diet. After six months of treatment they determinate by immunohistochemistry, the expression of the amyloid precursor protein in absorptive cells in the small intestine and observed a greater expression of this molecule in small intestinal epithelial cells of high-fat fed animals, whereas animals fasting 65 h did not show any expression. There is another study where the group of John CL Mamo evaluated the expression of Aβ in enterocytes after a low- or high-fat diet with 1% cholesterol in apoliprotein E (apo E) (-/-) knockout mice. Apoliprotein E is a lipoprotein that modulates Aβ biogenesis [12–14]. After six months of dietary treatment, the small intestine of apo E (-/-) KO mice fed with low-fat diet showed the same levels of expression of Aβ as the wild-type animals detected by immunohistochemistry. On the other hand, both groups of animals, wild-type and apo E (-/-) KO mice fed with high-fat diet, showed an increased expression of Aβ in enterocytes being higher in the KO animals. Also in these study, the group evaluates villi length between the groups treated, finding that the high-fat diet did not affect villi length in apo E(-/-) KO mice, but interestingly there is an increase in villi length of KO mice treated with low-fat diet when compared with wild-type mice under the same dietary conditions [15]. These groups also carried out a very elegant study to corroborate the association of Aβ production with recently generated lipoproteins, employing three-dimensional immunofluorescence microscopy and determinated that Aβ produced by enterocytes certainly has a clear colocalization with chylomicrons in small intestine enterocyte after three months of dietary treatment (free of cholesterol). They found that the amount of Aβ colocalizing with chylomicrons reaches the double [16]. These data together confirms the presence of Aβ in

lipoproteins generated in small intestine and that a diet rich in fat could increase the production of transport lipoproteins. However, the open question stills remains: how this Aβ produced systemically reaches the brain? **(Figure 1)**. Further studies are necessary to establish if indeed an imbalance in lipids production induced by diet can promote the delivery of these systemic Aβ to brain and induce cerebral amyloidosis.

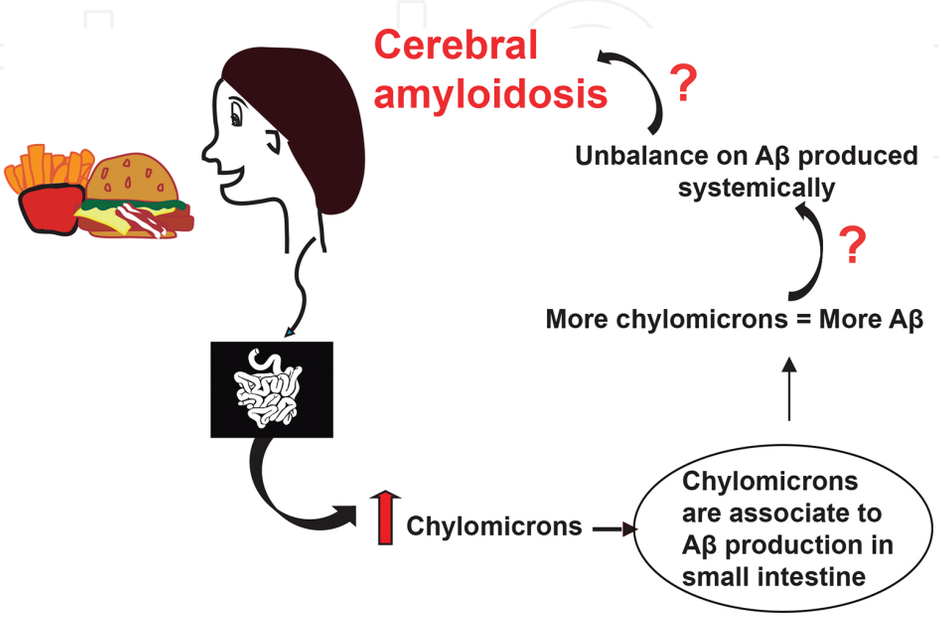

Figure 1. The ingestion of food rich on fat and cholesterol can increase the amount of postprandial lipoproteins chylomicrons. An increased production of chylomicrons can lead to an overproduction of A*β* and potentially produce an unbalance on A*β* processing and lead to cerebral amyloidosis.

3. Effect on vascularity and BBB integrity

The brain is a very well-protected organ with two barrier systems. One is a highly specialized microvascular endothelial system known as blood brain barrier (BBB), its function is to protect the brain from the entry of damaging substances and at the same time, allows the entry of nutrients as well as endocrine signals by means of an active transport and a passive diffusion system. The second is the choroid plexus, whose function is to prevent the entry of blood in the cerebrospinal circulation [17]. An unbalance in such systems could lead to disease conditions regarding the entrance of damaging molecules or disrupting the entrance of proper nutrients or endocrine signals. A good body of data has focused in study; how dietary habits can trigger BBB disruption? A longitudinal study, carried out in Sweden, evaluated the integrity of BBB *in vivo* in 81 women with a wide range of body size, who acceded to receive a lumbar puncture in order to obtain cerebrospinal fluid and compared the index of albumin content. Albumin is a constitutive protein that is absent in the brain, since its access is stopped by the BBB; therefore its presence in cerebrospinal fluid is a sign of disruption of the protection systems. Among these large group studied, the obese and overweight women between 70 and

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84 years had the highest amount of albumin reported as the ratio of albumin in cerebrospinal fluid/Serum albumin (CSF/S albumin). Interestingly, they found a correlation between low levels of sex hormone binding globulin (SHBG) in the same group of women when they were younger [18]. It is known that SHBG decreases with overweight in both, male and female [19–21]. In the Swedish longitudinal study, SHBG was employed as measure of endocrine signal in the same group of females when they were in there middle forties, and decades later when they were analyzed for several parameters besides the CSF/S albumin ratio, such measures included behavioral evaluations finding that they had cognitive alterations [18]. It strongly suggests that since youth, these group of obese and overweighting women had less content of SHBG accompanied in elderly years by BBB disruption and cognitive decline. These data suggest that an unbalance between the selective entrance and exit of molecules and signaling drived by a failed BBB filtering can lead to development of dementia, but more experimental data is needed in order to elucidate the mechanism behind this effect. One way to explain the cognitive detriment found in these patients could be the diminishment of factors that have been shown to be protective for the brain, such as SHBG. High levels of SHBG have been associated with neuroprotection in stroke, vascular and cardiovascular diseases, diabetes [21–25], and an increased amount of molecules potentially damaging for the brain, such as Aβ [26–28]. Such idea can be supported by the fact that it was found in the obese and overweight women, a higher ratio of CSF/S albumin has been observed in subjects with AD as well [29, 30]. In this study, the CSF/S albumin content was measured in 118 patients diagnosed with AD and clinical data of vascular alterations was registered as well. The AD subjects were compared with individuals without dementia of the same age, finding a higher albumin ratio in those with both AD and vascular factors. There was not significant BBB disruption in the patients without vascular alterations; additionally, there is no correlation with BBB disturbances and age in the control group, which strongly suggests a relationship with the vascular alterations, BBB disruption, and AD [29]. Controversially in a study, albumin content as well as IgG in serum and cerebrospinal fluid in several groups of patients with different dementias such as early-progression familial AD, the senile dementia of Alzheimer type (Late Onset Alzherimer's Disease LOAD), and two types of vascular dementia: a group diagnose with vascular dementia and others with multiinfarct, were measured. The multiinfarct group was reported with the highest significant alteration of the BBB but not in AD group. All these data supports the idea that vascular factors associated to BBB disruption are in relationship with the development of many dementia syndromes and are not restricted to AD [31]. That controversial information can be clarified with animal experimental data, where several variables can be controlled. The very first experimental evidence that the Aβ peptide can actually cross BBB and be deposited in the brain parenchyma was done in 1993 by Zlokovic et al. [32]. The researchers injected synthetic forms of Aβ peptide: 1–28 and 1–40, which were labeled with a radioactive marker in order to follow it after carrying out an injection in the neck vessel of the guinea pigs. The research group found a specific deposition of both synthetic peptides in the BBB microvasculature, initiating in the luminal side and transcellular transport into the brain parenchyma. This study strongly supports the idea that the Aβ produced systemically can cross the BBB. However, the mechanism remains unclear so far.

Although there is evidence that BBB can be disrupted in patients with dementia, it is possible that the development on AD can be due to systemically produced Aβ that can cross the BBB and form the deposits in the brain, but how does this happen? As we reviewed, obese patients apparently have a disrupted BBB permeability, although, what triggers that? Are the intake habits involved in such phenomenon? There is experimental evidence that suggest that components of Western diet, such as cholesterol and saturated fat, can contribute to that phenomenon. Studies with rabbits fed with a diet containing 2% cholesterol for 8 weeks, have demonstrated that such type of diet disrupts BBB permeability, alters vascularity, and induce vessels inflammation and Aβ peptide accumulation in parenchyma [26–28]; and this accumulation is similar to that observed in brains of AD patients [33]. This body of data, mainly generated by D.L. Sparks and collaborators, strongly supports the idea that high cholesterol consumption, importantly, contributes to the development of AD onset by the accumulation of Aβ, vascular alterations, as well as BBB selective permeability disruption.

The contribution of BBB disruption of a high energetic diet (HE) (approximately 40% Kcal of fat versus 13% of standard laboratory rodent diet) based on high saturated fat and glucose was evaluated in 60-days-old 32 male rats that were fed for 90 days with this type of diet. The researchers evaluated the BBB integrity, measuring by ELISA, the content of sodium fluorescein (NaFl) injected throughout the femoral artery in the prefrontal cortex, striatum, and hippocampus of the treated rats. They found a significant increased amount of NaFl in the hippocampus of the treated rats compared with the control but not in prefrontal cortex or in striatum. They also measured the mRNA expression of tight junction proteins by RT-PCR in choroid plexus and BBB capillaries. Thigh junction proteins are critical components for maintenance of selective BBB permeability, its diminishment can alter the BBB function. They found a decrease expression of the thigh junction proteins and alterations in behavioral task directly associated with hippocampal function [1]. A further study was carried out by Davidson et al. [34], where they fed 24 male rats with a high energy diet as well as high saturated fat and glucose and following for different time points (7, 14, 21 and 28 days), evaluated BBB integrity by injecting NaFl following the same procedure reported by Kanoski et al. [1]. They found that the hippocampus was the brain structure that exhibit the highest concentration of the dye compared with prefrontal cortex and striatum. In this study, the researchers evaluate the differences between those animals, under HE diet, that show what they called *obesity resistant* versus those that developed obesity. The obesity resistant group was the one that consumed the HE diet but gained the least weight and body fat. The animals included in the obesity group were those that gained the most bodyweight and fat. It was this last group that showed the major BBB permeability and had the highest deposit of NaFl in the hippocampus. Interestingly, they found that those animals, in the HE diet, had the lowest bodyweight and the lowest amount of fat, and did not show difference in the behavioral performance compared with the control group. However, those rats that developed obesity and had the higher deposit of dye in the hippocampus, showed alterations in the performance of the hippocampal-dependent tasks [34]. These evidences directly shows a relationship between diets rich in fat, obesity development, and hippocampal-related cognitive alterations. We will discuss in the next section, the relevance of the hippocampal structure, cognitive performance, and its detriment.

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From the information reviewed in this section, we can conclude that BBB alteration is a feature that takes part of dementia onset in both, AD and vascular dementia. Obesity can contribute to this phenomenon and, although the mechanism is not well known, a particular factor that can participate in this process is the intake of diets rich in cholesterol or fat, as well as glucose, those known components of a typical Western diet **(Figure 2)**.

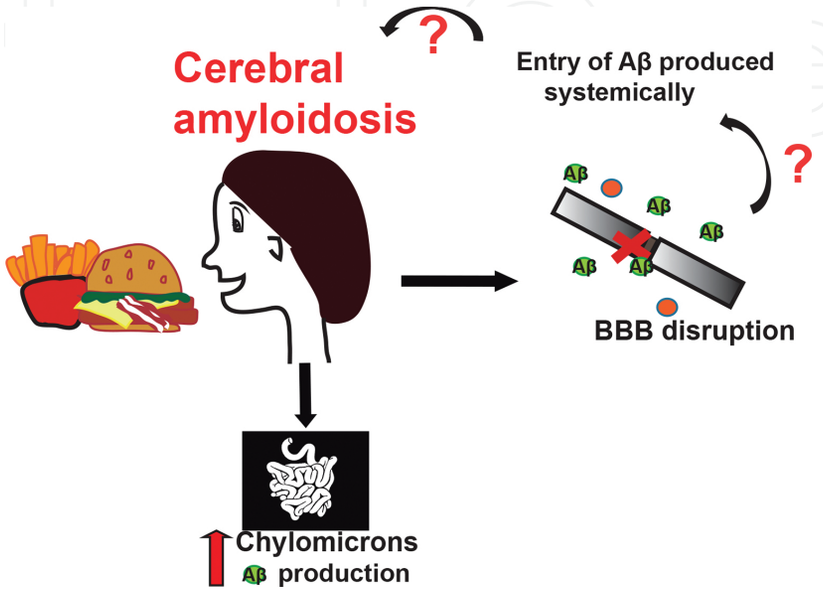

Figure 2. The overproduction of systemic Aβ, produced by consume diets rich on fat or cholesterol, can promote and alter the selective permeability of BBB, allowing the passage of molecules to the brain, such as systemic Aβ that was not clear and lead to cerebral amyloidosis and brain inflammation.

4. Impact of a diet rich in cholesterol or fat on the development of AD onset

The hippocampus is a brain structure considered as a part of the allocortex, which is one of the oldest brain areas from the phylogenetical point of view. It has a high capacity of plasticity; it is directly involved in learning and memory process and, interestingly, is very susceptible to damage and has attracted the research focus for several years since it is one of the first brain structures that degenerate during the AD process [35]. As we reviewed in the last section, the hippocampus seems to be very susceptible to the effect of consumed diets rich in fat or cholesterol, but can this actually drive the brain into a degenerative process? Can it contribute to the development of dementia? We will discuss this idea in the current section. First, we will review how the diet high in cholesterol or fat can contribute to the development of features associated with AD, particularly with amyloidosis.

Diets rich in cholesterol, as we have reviewed, can induce vascular inflammation, BBB, and promotes Aβ peptide accumulation in the brain parenchyma in an animal model of rabbit fed with high-cholesterol diet [26–28]. Supporting the association of elevated concentrations of cholesterol and AD detriment in a very recent *in vitro* study carried out by Avila-Muñoz and

Arias [36] in isolated astrocytes obtained from brain cortex of 1- to 3-day-old Wistar rats, they found astrocyte activation, An increase on the expression of amyloid precursor protein (APP), and promoted its amyloidogenic processing, and an increase in reactive species oxygen (ROS), a marker of oxidative stress, after treating the culture for 48 h with cholesterol concentrated at 25 or 50 μM. All these parameters measured, including glia activation, resemble features that have been found in postmortem brain tissues obtained from AD patients [37–39], but how the consumption of a diet high in cholesterol can contribute to the development of AD? *In vivo* studies can answer this question. Transgenic mice Tg2576 (which express the human APP695 carrying the Swedish double mutation at codons 595 and 596, Hsiao et al. [40]), were fed with a 5% cholesterol diet for 6 weeks. They found an increase of the APP cytosolic fragment but apparently the hypocholesteremia induced by the diet does not deregulates Aβ metabolism (George et al, 2004).

In a further work, carried out by Refolo et al [41], with 5-months-old double-mutant for presenilin (PS) and amyloid precursor protein (PSAPP) mice, which express familial mutant PS1M146V and the APP695 mutations [42], evaluated the effect of a combined diet with 5% cholesterol and 10% fat for 7 weeks. They found that the dietary treatment induced elevated levels of cholesterol in both, plasma and brain, which is an important data since it showed that brain cholesterol is produced *in situ*, and this data demonstrates that brain cholesterol is increased by diet. This increase in brain cholesterol correlates with an increase of total Aβ in brain. In addition, there was an enhanced amount of Aβ, particularly not in Aβ 1–40 and 1–42, but in 1–30 and 1–34 as well. This was accompanied with an increase in the number of Aβ deposits as well as an increase in the plaque area in the hypercholesteremic transgenic mice. Interestingly, there were no changes found in presenilin 1 (PS1) processing. These data strongly supported the hypothesis that a diet high in fat and cholesterol can contribute to the development of amyloidosis, one of the main conditions to develop AD.

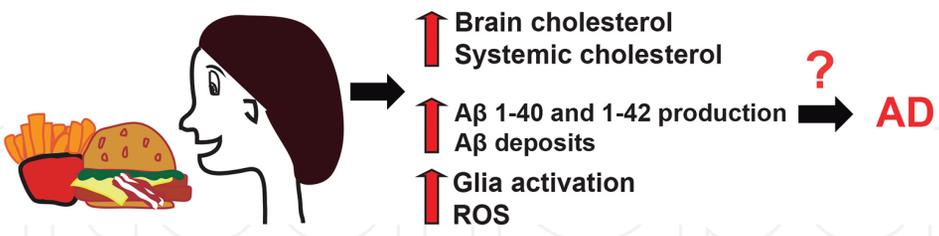

Figure 3. As result of consume diets high on fat and cholesterol there is an increase levels of brain cholesterol and systemic cholesterol. Also elevates A*β* production in brain and its deposit and increases as well the glia activation and production of ROS in brain. All these together can lead to AD onset.

All these data shows experimental evidence linking the consumption of diets rich in fat and/or cholesterol with the development of amyloidosis. Nevertheless, dementia is a more complex syndrome, comprised of many other features such as cognitive decline and neuronal lost. Particularly in the hippocampus, which is as we mentioned before, one of the first areas affected during the neurodegenerative process, its susceptibility to suffer alterations resulted from consuming diets high in fat or cholesterol appears crucial as one of the possible mecha-

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nism involved in the development of AD **(Figure 3)**. We will discuss that idea in the section below.

5. Impact on brain morphology, plasticity, and cognition

In the last sections, we have discussed how the consumption of diets rich in fat or cholesterol can contribute to the production of Aβ peptide in noncerebral tissue. The impact that this could have in the BBB selective permeability and its participation in brain amyloidosis conditions that can contribute to the dementia onset but, besides these alterations, one of the main conditions found in dementia patients is brain atrophy and behavioral alterations. Is brain functionality affected by the components typically found in the Western diet? Could diet composition affect brain architecture and plasticity? Moreover, is cognition affected the consumption of diets rich in fat or cholesterol? We will review such ideas in the current section.

A link between cognitive decline and dietary habits has been proposed. There is an epidemiological study carried out with Japanese men living in Hawaii compared with age-matched men living in Japan that evaluated the prevalence of dementia employing the Diagnostic and Statistical Manual of Mental Disorders. The results found that those subjects living in the USA have a higher prevalence of dementia: 9.3% for all type dementia, 5.4% for Alzheimer's disease, and 4.2% for vascular [43]. Continuing in this line of evidence, there is another study that was carried out with people from same ethnic background living in their natal land or in a foreign country (USA). They found in concordance with the study cited before, that those individual living in Indiana (where the study was carried out on) had a higher prevalence of dementia compared with age-matched individuals living in Nigeria or Ibadan [44]. This data strongly suggests that there are some stimuli in this Western country, which contribute to the development of several types of dementia, and the question is: what are these stimuli? A good candidate are the nutritional habits. In Western countries, especially countries such as the USA or Mexico, people consume food with high amounts of saturated fat and cholesterol and show the highest rates of obesity worldwide. The brain is an organ rich in lipids and essential fatty acids that are mainly obtained from food and have a crucial participation on brain functioning [45]. So, to think that lipids elevation induced by diet could be in detriment of the brain, which is a logical assumption, but what are the cellular mechanisms involved in the possible detrimental effect of food components such as fat and cholesterol? Well, experimental work has demonstrated evidence of the interplay between obesity, brain alteration, and cognitive decline, more especially with hippocampal-related cognitive processes. Seminal works in this area were carried out in the University of Toronto by Greenwood and Winocur [46]. They fed 1-month-old Long-Evans rats with two types of high-fat diets containing 40% of calories: a saturated fatty acids (lard-based) or a polyunsaturated fatty acids (soybean oil-based) and compared with a standard laboratory diet containing 4.5% of fat. They tested learning and memory abilities in the rats after 3 months of dietary treatment with the radial arm maze test, the variable-interval delayed alternation task, and the Hebb-Williams maze series. These tests evaluate spatial learning and memory performance and report failures in working or reference memories. They found that those animals fed with the lard-based diet showed impairment in

all the tests. Following this line of evidence, they analyzed further with different types of saturated fatty acid diets: monounsaturated (MUFA) and polyunsaturated (PUFA) fatty acids, finding a direct relationship between the 3 months consumption of saturated fatty acids and failures in basic alternation rule, and remembering trial-specific information over time in the variable-interval delayed alternation task. Interestingly, they found alterations in brain's phosphatidylcholine fatty acid profile. However, the changes in the membrane did not correlate with cognitive alterations [47]. It suggested there is another mechanism elucidating the cognitive impairment related to consumption of diets rich in fat; a good candidate is brain inflammation. Chronic inflammation is one of the principal altered events associated with AD [48], and it has been linked to obesity and has been reported that there is a correlation between both, obesity and AD [49, 50]. Middle-aged C57BL6 male mice were fed for 21 weeks with chow equivalent to Western diet containing 41% fat or a high-fat lard diet containing 60% fat for 16 weeks. They showed an alteration on learning acquisition measured by the Stone T-maze and it is accompanied by microglial activation, increase expression of cytokines like TNFα, IL-6, and MCP-1, and a decrease on brain-derivated neurotrophic factor (BNDF) [51]. Interestingly, there was not any detrimental effect observed in those animals that consumed the like-Western diet. These data agree with results from Greenwood and Winocur and propose a possible way underlying the effect diet, which is an inflammation process, and the decrease on neural factors crucial for learning processes. The results demonstrate that diet can interfere with learning abilities, but is it everything behind the diet effect on cognitive decline? There is a report with 344 white middle-aged male Fischer rats. The researchers evaluate the effect of a diet high in cholesterol and fat (diet containing 2% cholesterol and 10% hydrogenated coconut oil). The results showed a failure in working memory, here evaluated with the water radial arm maze as well as elevated lipids profile and reduce expression of Map-2 as an indicator of alteration of dendritic integrity, which correlates with memory mistakes measured in the test, and increase in inflammation markers such as microglia activation [52]. In a study carried out with Sprague-Dawley rats, which were fed for 7 days with high fat and fructose, several hippocampal alterations, such as decreased insulin signaling, were reported. In addition, they found that treated animals had a decrease in hippocampus total weight in addition with some other morphological alterations such as a diminishment on the number of dendritic spines and a reduction in the complexity of the hippocampal dendritic arborization. Moreover, there was a decrease in the expression of the microtubule-associated protein 2 (MAP-2) and in the content of synaptophysin in the CA1 region concomitant with an increased phosphorylation of tau protein, and in the presence of reactive astrocyte associated [53]. It directly demonstrates alterations in hippocampal cytoarchitecture that definitively have a strong impact on brain functionality, especially in hippocampal-related learning and memory processes.

Another feature which affected by consuming diets rich in fat is adult hippocampal neurogenesis (AHN). Adult neurogenesis is a highly specialized plasticity phenomenon that, under basal conditions, occurs in two restricted brain areas: a) the subventricular zone and b) the hippocampal dentate gyrus [54, 55]. Hippocampus is a crucial area for memory processes, since its decrease is associated to memory failures, especially in short-term memory, spatial memory, and learning flexibility [56–59]. The AHN is a complex process that comprises several devel-

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opmental steps starting from the division of an endogenous neural precursor cell followed by its expansion, differentiation, and fully integration to the hippocampal network [60]. These steps are reported as number of proliferative cells measured by markers of cell division; cell fate decision with the marker of early differentiation, the cytoeskeleton protein doublecortin (DCX) that is expressed in newly differentiated cells, and with NeuN, a nuclear marker of granular cells when the cell is fully differentiated. It has been recently documented that there are some food components which can regulate the neurogenic process (for a review [61]). The hippocampal neurogenesis has captured the attention since it was described in 1965 by Dass and Altman [62] due, as we already mentioned, the hippocampus is closely related to memory as well as neurodegenerative processes. Juvenile male and female Sprague-Dawley rats under a dietary regimen of high- (42% coconut butter and corn oil fat) or low-fat diet (10% fat by energy) or standard laboratory chow for 4 weeks, was found that males under high-fat diet show less cell proliferation than females and reported elevated levels of corticosterone, a stress hormone [63]. Differences in AHN were studied in mice susceptible to develop obesity (C57BL/6N) and obesity resistant (C3H/HeN). They were fed with high- and low-fat diet finding that those animals that developed obesity and consumed the high-fat diet had much lower number of proliferative cells and cells committed to neural linage (DCX positive cells), which establish a clear link between obesity and AHN diminishment [64]. In our laboratory, we have observed that 8 weeks of diet rich in fat (60%) or high in cholesterol (1.4%) in 5-months-old male Wistar rats has an impact on AHN in both, cell proliferation and more especially in the morphology of DCX cells. These cell populations have less processes and a poor complexity than animals under normal laboratory diet, and we found alterations in short-term memory (Leal-Galicia and Meraz-Ríos data *not yet published*). All these data together strongly suggest a detrimental effect on diets rich in fat or cholesterol in cognitive components such as navigation memory, working memory, acquisition learning, and short-term memory suggesting as mediators, alterations in brain cytoarchitecture and AHN, and associates obesity with such cognitive alterations strongly supporting the hypothesis that obesity can lead to development of dementia **(Figure 4)**.

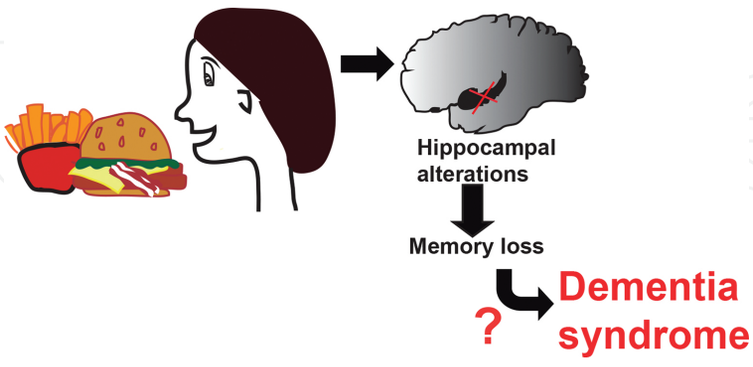

Figure 4. The intake of food with high amounts of fat or cholesterol produces alteration in the hippocampus such as: reduced expression of Map-2, reduction on the number of dendritic spines and in the complexity of the dendritic tree and a decrease on neurogenesis. Consume diets with these components has also a functional impact in short-term memory, working memory and learning flexibility, that could contribute to the detriment observed in the dementia syndrome.

6. Conclusion

The consumption of diets rich in cholesterol, fat, as well as another components (carbohydrates) of the so called "Western diet" can contribute to increase the production of the peptide Aβ. This could contribute to brain amyloidosis by means of alteration of the selective permeability of the BBB, since BBB alterations are induced for these type of diets. In addition, it has been shown in the brain of transgenic animals that the amyloidosis can be accelerated by the intake of fat or cholesterol, which can lead to accumulation of Aβ in the brain. Besides that, the intake of fat or cholesterol can induce alterations in brain morphology and plasticity accompanied by a detrimental in cognitive abilities in animal models that resemble those alterations in cognitive abilities reported in AD patients, such as short-term memory, working memory, and learning flexibility. These evidences strongly suggest an association with the dietary habits and the possible development of AD in both cases, Early Onset Alzheimer's Disease or Late Onset Alzheimer's Disease, and a connection with systemic disruptions and brain functions **(Figure 5)**.

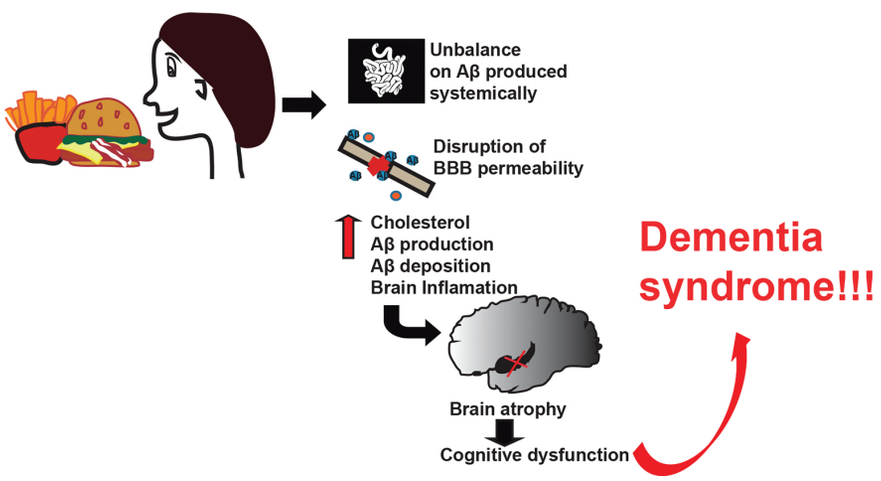

Figure 5. Diets rich on fat or cholesterol that are widely consume in Western countries can lead to develop dementia onset for several ways. One is the overproduction of systemic A*β* that can reach the brain due the chronic consume of these food components can affect the selective permeability of BBB. It can facilitate the pass of systemic A*β* as well as another molecules producing brain inflammation and A*β* deposits. It is accompanied for alterations in hippocampal plasticity and its cytoarchitecture. That can have an impact on brain functionality observed as memory failures. All these together can contribute to the development of dementia.

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