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Impact of fatty acids on brain circulation, structure and function

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ABSTRACT

The use of dietary intervention has evolved into a promising approach to prevent the onset and progression of brain diseases. The positive relationship between intake of omega-3 long chain polyunsaturated fatty acids (ω3-LCPUFAs) and decreased onset of disease- and aging-related deterioration of brain health is increasingly endorsed across epidemiological and diet-interventional studies. Promising results are found regarding to the protection of proper brain circulation, structure and functionality in healthy and diseased humans and animal models. These include enhanced cerebral blood flow (CBF), white and gray matter integrity, and improved cognitive functioning, and are possibly mediated through increased neurovascular coupling, neuroprotection and neuronal plasticity, respectively. Contrary, studies investigating diets high in saturated fats provide opposite results, which may eventually lead to irreversible damage. Studies like these are of great importance given the high incidence of obesity caused by the increased and decreased consumption of respectively saturated fats and ω3-LCPUFAs in the Western civilization. This paper will review *in vivo* research conducted on the effects of ω3-LCPUFAs and saturated fatty acids on integrity (circulation, structure and function) of the young, aging and diseased brain.

Contents

1. Introduction

Paleontological studies have shown that feeding habits played a crucial role in the development of the human brain [1]. Differences in diet among primates affected survival rate and the ability to reproduce, which are both related to brain size and cognitive functioning [2]. It is now known that brain size increased with the development of skills that required proper cognition, such as cooking and access to food and this led to the formation of the modern brain as we know now [3]. An evident example of diet effects on the brain was observed when comparing encephalisation (increasing brain/body-mass ratio) of hominids (early humans) living close to the shore with that of hominids living in-land [4]. A shore-based diet, which included high consumption

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of fish, led to extensive encephalisation in this population. This is probably related to the higher consumption of omega-3 fatty acids like docosahexaenoic acid (DHA; 22:6$n-3$) in this shore-based diet, as DHA is an important brain constituent present in cell membranes but cannot be synthesized efficiently by the human body itself.

When we analyze the situation now-a-days, a similar comparison can be made: with on one side a 'Mediterranean-type diet' and on the other side a 'Western-type diet'. The conception of a Mediterranean-type diet (which is rich in long-chain polyunsaturated fatty acids) is derived from the combination of high intake of fruits, vegetables, nuts, cereals, olives and olive oil and more fish; less milk but more cheese; less meat; and moderate amounts of wine [5]. On the other hand, a Western-type diet is the result of increased saturated and *trans* fatty acids consumption due to introduction of food staples and food-processing procedures after the Industrial Revolution [6]. This difference in diet is reflected in an increased death rate caused by cancer and heart disease in the United States compared to Crete, which are characterized by consuming a Western-type diet and Mediterranean-type diet, respectively [7]. Outcome of cancer and heart disease is clearly affected by different diets and their effect on the cardiovascular system [8]. Cardiovascular risk factors are considered important risk factors for the onset of neurological diseases such as stroke and Alzheimer's Disease (AD). The focus of this review will be on the effects of dietary components on the brain as there is abundant data available revealing the effects of specific diet components on brain health and mental functioning [9]. For example, high serum cholesterol levels, possibly via dietary intake of high saturated fat, in midlife increases the risk of AD in later life while a diet low in saturated fat like the Mediterranean diet is inversely related to this [10,11]. Several groups tested the possibilities to slow down the progression of diseases like AD with nutrition-based intervention in animals and humans. Experimental data revealing the influence of diet components on three important indicators of brain health: (1) circulation, (2) structure and (3) function, will be highlighted in the present review. In this context, we will mainly emphasize the effects of omega-3 long-chain polyunsaturated fatty acids (ω3-LCPUFAs) on these aspects and compare this with the evidence found concerning the intake of saturated fatty acids. Obtaining more knowledge concerning the aftermaths of malnutrition on the brain is necessary since diseases like obesity, metabolic syndrome and diabetes gain prevalence in modern society.

2. Circulation

Due to high demands of energy by the brain and its low capacity to store this energy, the brain is the most highly perfused part of the human body [12]. Proper functioning, including adequate cerebral blood flow (CBF) and vessel reactivity, is necessary to ensure the microenvironment in which brain cells function efficiently. The importance of proper cerebral circulation is reflected in cerebrovascular and neurodegenerative diseases such as atherosclerosis, stroke and AD. Higher cerebral perfusion and the ability to restore blood flow rapidly will lead to a lower amount of cell death after a stroke, resulting in less functional impairment eventually [13]. In addition, more and more evidence points towards a vascular basis of the pathologies observed in AD [14]. For example, AD patients show reduced CBF and cerebrovascular reactivity compared with healthy age-matched control subjects [15,16]. Moreover, Zerbi et al. (2013) showed a reduced microvascular relative cerebral blood volume in the cortical, thalamic and hippocampal brain regions of APPswe/PS1dE9 Alzheimer mice [17,18]. Sedentary lifestyle characterized by high saturated fat intake is linked to increased onset of dementia while moderate intake of unsaturated fat is associated with a decreased risk of dementia [10,11], confirming the potential role of diet on underlying pathological mechanisms such as impaired brain circulation.

2.1. Diet effects

Indeed, fundamental studies have shown that high-fat intake negatively affects vascular functioning through increased myogenic tone and endothelial dysfunctioning, both important properties in regulating CBF [19–22]. In principle, adequate CBF is regulated via two mechanisms: autoregulation and neurovascular coupling (NVC) [23]. Cerebral autoregulation is responsible for maintaining optimal and stable CBF during normal activities by counteracting changes in arterial pressure through arterial relaxation and constriction (i.e. vascular tone) [24]. Contrary, NVC plays a pivotal role in increasing flow in regions that display increased functional neuronal activity. Experiments with hypercholesterolemic ApoE$^{-/-}$ mice fed with a high-fat diet (20% fat) showed higher cholesterol plasma levels and impaired endothelium-dependent dilator responses of cerebral arterioles in these animal, compared to normocholesterolemic ApoE$^{-/-}$ mice [20]. This is presumably caused by increased production of reactive oxygen species (ROS) leading to vascular changes such as impaired regulation of vascular tone [19,22]. Similar differences were also observed in non-transgenic Wistar rats. The high-fat diet (45% fat) significantly attenuated the change in cerebral blood flow after whisker stimulation in these animals. This reduction in cerebral blood flow response may be caused by impaired K+-induced vasodilation since this was significantly reduced in the high-fat (45%) diet group compared to rats on control diet (10% fat) rats [21]. Taken together, these differences demonstrate impaired coupling between neuronal and vascular cells due to high dietary-intake of fat. While studies that utilize high-fat diets, containing high levels of saturated and *trans* fatty acids, indicate impaired neurovascular mechanisms, supplementation with ω3-LCPUFAs like DHA and eicosapentaenoic acid (EPA; 20:5$n-3$) suggests contrary effects [25–27]. Aged monkeys that were given DHA-enriched soymilk for 1 week or for 4 weeks showed significantly increased regional cerebral blood flow (rCBF) in the somatosensory cortex after vibrotactile stimulation compared with the control group that was given soymilk solely [27]. Injection of the DHA and EPA precursor α-linolenic acid (ALA; 18:3$n-3$) improved local CBF rates in rats by almost 20% compared to the saturated fatty acids palmitate [28,29]. A special diet composed of DHA, EPA and Uridine monophosphate (DEU; all important precursors of membrane components [30]) significantly increased CBF in the cortex and thalamus of APPswe/PS1dE9 Alzheimer mice [17]. In line with these data, increased regional cerebral blood volume (rCBV) was also observed by our group in wildtype mice after treatment for 8 weeks with a DHA and EPA enriched diet [25]. In addition, long-term consumption (~9 months) of a multi-nutrient (Fortasyn™ Connect; FC) diet by wildtype and ApoE$^{-/-}$ mice initiated locally increased CBV values. These changes were especially observed in regions close to brain feeding arteries [31]. Compared to the DEU diet, the FC diet included additional nutrients such as choline, phospholipids, vitamins and antioxidants, which are all important co-factors for maintaining neuronal membrane health through the Kennedy Cycle [32]. Human data on modulation of cerebral circulation such as CBV and CBF by dietary components are scarce but available results confirm the detrimental and beneficial effects of high-fat diet and DHA found in animal studies, respectively. To our knowledge, no study is available that showed changes in CBF due to high-fat intake in human in which no metabolic disorder is present. Nevertheless, obese women (mean BMI of 32.7) showed decreased rCBF during