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Diet and cognition: interplay between cell metabolism and neuronal plasticity

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Abstract

Purpose of Study—To discuss studies in humans and animals revealing the ability of foods to benefit the brain: new information with regards to mechanisms of action and the treatment of neurological and psychiatric disorders.

Recent Findings—Dietary factors exert their effects on the brain by affecting molecular events related to the management of energy metabolism and synaptic plasticity. Energy metabolism influences neuronal function, neuronal signaling, and synaptic plasticity, ultimately affecting mental health. Epigenetic regulation of neuronal plasticity appears as an important mechanism by which foods can prolong their effects on long term neuronal plasticity.

Summary—The prime focus of the discussion is to emphasize the role of cell metabolism as a mediator for the action of foods on the brain. Oxidative stress promotes damage to phospholipids present in the plasma membrane such as the omega-3 fatty acid DHA, disrupting neuronal signaling. Thus, dietary DHA seems crucial for supporting plasma membrane function, interneuronal signaling, and cognition. The dual action of brain-derived neurotrophic factor (BDNF) in neuronal metabolism and synaptic plasticity is crucial for activating signaling cascades under the action of diet and other environmental factors, using mechanisms of epigenetic regulation.

Keywords

Epigenetics; Membrane Fluidity; Omega-3 fatty acids; Polyphenols; Metabolic Syndrome; Exercise

Introduction

Poor dietary habits are likely contributors to the surge of neurological and psychiatric disorders in the last decade. In particular, the consumption of high-calorie diets is garnering special recognition as risk factor for impaired cognitive function and emotional health (reviewed in Ref. [1]. Understanding of the molecular basis for diet action on brain function will help to develop cost-effective therapeutic strategies for the protection against

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deleterious consequences of multiple neurological and psychiatric disorders. Energy efficiency has been a primordial factor for biological adaptation, and new studies show that this property is operational for supporting cellular events involved in cognitive function [2]. As discussed below, dietary factors like omega-3 fatty acids and polyphenols act as important energy modulators during cognitive operations. Environmental factors may contribute to build a long-term reserve to support brain function and cognition during challenging situations such as aging or disease (Figure 1).

Metabolic profiling and Neuropsychiatric disorders

An increasing body of information indicates an association between metabolic abnormalities and the incidence of neurological and psychiatric disorders (reviewed in [3–6]). The brain has an extraordinary high metabolic rate, as it consumes about 20% of oxygen inspired at rest, while accounting for only 2% of the body weight. This immense metabolic demand is because neurons need large amounts of ATP for maintenance of ionic gradients across the cell membranes to support neurotransmission. Since most neuronal ATP is generated by oxidative metabolism, neurons critically depend on mitochondrial function and oxygen supply. Neuronal function and survival are very sensitive to mitochondrial dysfunction [7] such that mitochondrial dysfunction is a factor in the pathology of acute insults like ischemia-reperfusion injury and in chronic neurodegenerative disorders like Alzheimer's and Parkinson's disease [8]. The interplay between mitochondrial function, energy metabolism, and neuronal activity is of critical importance for understanding the pathophysiology of various neurological diseases.

How metabolic aberrations harm the brain

The metabolic syndrome (MetS), defined as a cluster of disorders including obesity and diabetes, is reaching epidemic levels in the American population, and the prospect that it can reduce neurological function is alarming. The weaknesses imposed by the MetS are particularly alarming if we consider that the pathology of most brain disorders has some failure in the capacity of neurons to metabolize energy [9,10]. Dietary factors such as increasing consumption of fructose is considered as an important contributor to the MetS in humans [11], and rodents treated with high fructose diet display signs of MetS such as increased hepatic lipid and triglyceride level [12], and peripheral insulin resistance [13]. Fructose-induced MetS reduces synaptic plasticity and learning and memory performance in animals [14] (Figure 2), and alter molecules which play important roles in mitochondrial bioenergetics [15]. MetS disrupts signaling through insulin receptors which are strategically localized to brain areas involved in cognitive processing such as the hippocampus [16]. Deficiency of dietary omega-3-fatty acids has been shown to predispose the brain to disturbances in insulin signaling that may be considered a risk factor for diabetes [14]. It has also been shown that omega-3 dietary deficiency during brain formation and maturity exacerbates the effects of metabolic disorders on the adult brain [17]. These studies suggest that maternal diet can program offspring growth and metabolic pathways, which can further alter lifelong susceptibility to metabolic disorders.

Oxidative damage to plasma membrane, neuronal signaling, and cognition

The plasma membrane is highly susceptible to metabolic aberrations [18], and its malfunction can compromise neuronal signaling, lowering the threshold for many diseases. Particularly, neuronal membranes are composed of a lipid bilayer, in which, docosahexaenoic acid (DHA) is the most abundant phospholipid in the brain [1]. Due to the high susceptibility of phospholipid to be oxidized, the plasma membrane can be easily affected my alteration of mitochondrial activity. For example, 4-Hydroxy-2-nonenal (4-HNE), a major aldehydic lipid peroxidation product of omega-6 polyunsaturated fatty acids is considered as a key mediator of oxidative damage-induced mitochondrial failure. 4-HNE binds a number of brain mitochondrial proteins during the initial hours after injury conditions [19, 20]. Studies have shown that low, basal levels of the 4HNE, present in cells, may act as a signaling molecule [21]. However, under conditions of oxidative stress, uncontrolled production of the lipid aldehyde may saturate metabolic pathways, yielding neuronal dysfunction or death. High fructose consumption disrupts membrane homeostasis, as evidenced by an increase in the levels of 4-hydroxynonenal (4-HNE). However, dietary n-3 fatty acids have the potential to counteract MetS effects on brain by promoting membrane homeostasis [14].

The ability of the plasma membrane to transmit interneuronal signals relies on its fluidity, which is determined by its level of saturation and cholesterol content, among other factors [22]. Omega-3 polyunsaturated fatty acids (PUFA) such as DHA and eicosapentaenoic acid (EPA) significantly increase the unsaturation index and fluidity of membranes, while monounsaturated and saturated fatty acids do the opposite [23]. Additionally, omega-3 fatty acids can moderate cholesterol-induced reductions in membrane fluidity by displacing cholesterol from the membrane [22]. Lipid rafts are specialized glycolipoprotein domains along the membrane with the capacity to modulate cell communication through embedded protein receptors [24]. Studies demonstrate that PUFA like DHA augment the packing of protein receptors in these microdomains [25,26], thus portraying DHA as a critical element for modulating interneuronal communication. It is noteworthy that the metabolism of omega-6- fatty acids such as arachidonic acid (AA) is coordinated with that of DHA, and this interaction is critical for the regulation of membrane function, such that an elevation in the ratio of omega-6/omega-3 fatty acids poses a risk for chronic diseases [27]. Dietary DHA supplementation for eight weeks in rodents has been shown to attenuate an age-related decline in cognitive function, in conjunction with reducing AA-containing species and normalizing the unsaturation index in the brain [28].

Diet as a strategy to counteract the effects of MetS

It is difficult to treat Mets with confined strategies since its pathology is a cluster of disorders, such that approaches that would target several aspects of the pathology are intuitively more efficacious. The various positive actions of DHA in the body and brain [1] suggest that DHA is particularly suitable to defend against the broad pathology of MetS. Due to the facts that DHA is a structural component of plasma membranes in the brain and highly susceptible to oxidative damage, proper DHA function is crucial to maintain neuronal signaling. As discussed above, oxidative damage to the plasma membrane can be extremely

devastating as most receptors are embedded in the membrane, with the capacity to disrupt all forms of neuronal communication. There is large disparity with regards to the recommended levels of DHA in humans based on the many actions of DHA and different formulations. A number of studies have shown a varied range of n-3 intake to be beneficial for mental health (29), however it depends on the length of supplementation and likely affected by the baseline levels.

Polyphenols are a large family of compounds produced by plants to protect themselves against pathogen attacks and ultraviolet radiation. Curcuminoids and flavonoids are the main polyphenol subtypes with demonstrated actions on the brain. Polyphenols possess the capacity to attenuate cognitive deficits and support several neuronal processes such as synaptic plasticity [30]. Current trends point to the possibility that the powerful actions of polyphenols as antioxidants and anti-inflammatory molecules stem from their ability to support energy homeostasis (reviewed in Ref. [30,31]. Curcumin, the active component of the plant turmeric, has a long culinary and medicinal tradition in India [32] and has lately received ample attention because of its beneficial effects counteracting neurodegeneration in models of brain trauma [33] and Alzheimer's disease [34]. There is substantial evidence indicating that curcumin has strong antioxidant capacity exerted by increasing free radical scavengers and reducing lipid peroxidation [35]. Recent studies indicate that curcumin affects molecular systems involved with the metabolism of cell energy, and that its therapeutic effects on animal models of brain trauma may be exerted by restoring energy homeostasis [33,36,37]. Resveratrol is another polyphenolic component that is abundant in berries, grapes, and red wine, and has been found to protect neurons against Abeta-induced toxicity and attenuate behavioral impairment in rats [38]. The action of resveratrol in neurons has been compared to effects of energy restriction as resveratrol acts on the molecular machinery that control energy homeostasis [39]. Based on recommendations by the dietary supplement industry, the advised consumption of some major polyphenols such as isoflavones, quercetin, resveratrol and grape seed extracts (rich in proanthocyanidins) are 50 mg/day, 300 mg/day, 20 mg/day and 100–300 mg/day respectively (40) however these recommendations are not specific for brain functions. Consequently, future research about clinical applications of dietary polyphenols in neurodegenerative disorders is required.

From Metabolism to neuronal plasticity -- BDNF

Brain-derived neurotrophic factor (BDNF) is very susceptible to the effects of dietary manipulations such that diets rich in omega-3 fatty acids upregulate BDNF while high energy diets do the opposite [41]. BDNF deserves special consideration based on its newly discovered roles as a molecule that works at the interface of metabolism and synaptic plasticity [42]. An increasing body of research indicates that BDNF may serve in the process by which energy metabolism exerts a strong impact on synaptic plasticity and cognitive function [43]. BDNF is well recognized for its ability to facilitate the transmission of information across the synapse [44]. It may act as a mediator in the process by which the management of energy by the hypothalamus impacts cognitive centers such as the hippocampus [45]. BDNF can stimulate the mitochondrial activator PGC-1α in neurons, and PGC-1α plays a pivotal role in the formation and maintenance of synapses [46]. The capacity of metabolic signals to modulate synaptic plasticity and higher order processing

harmonizes well with the several roles of BDNF on cognition and emotions. For example, deletion of the *Bdnf* allele has been shown to increase anxiety-like behavior and promote cognitive deficits in mice [47] while the absence of the BDNF receptor TrkB was found to increase anxiety-like behavior in children and adults [48]. A separate line of studies has documented the importance of BDNF in human cognition, as to a polymorphism in the *Bdnf* gene is associated with an increased risk of cognitive impairment progression [49].

Metabolism and Epigenetics

Epidemiological studies suggest the capacity of dietary habits to influence the risk of metabolic diseases such as diabetes across generations (reviewed in Ref. [50]. A new line of studies indicates that the pathobiology of several psychiatric disorders such as depression may reside in epigenetic modifications of the genome [51,52]. Epigenetic phenomena are heritable and modifiable marks that regulate gene transcription without altering the underlying DNA sequence [53]. Epigenetic modifications include chromatin remodeling, histone tail modifications, DNA methylation and, more recently, have expanded to include non-coding RNA and microRNA gene regulation [54]. These are critical from embryonic development through the aging process, while aberrations in epigenetic patterns are emerging as etiological mechanisms in many age-related diseases such as cancer, cardiovascular diseases (CVD) and neurodegenerative disorders. Dietary factors can affect epigenetic mechanisms at multiple levels [53]. First, nutrients act as a source of methyl groups or as co-enzymes for one-carbon metabolism that regulates methyl transfer [55]. Second, nutrients and bioactive food components can directly affect enzymes that catalyse DNA methylation and histone modifications [53]. Third, diet is the ultimate input determining systemic metabolism which modifies cellular milieu leading to alterations in epigenetic patterns [56]. Modifications of the chromatin, involving DNA methylation and histone acetylation may be a vehicle by which the environment affects cognitive function and emotions by acting on the epigenome. For example, chronic administration of a diet rich in saturated fats and sugar has been shown to increase DNA methylation of the opioid receptor in the context of reward-related behavior [57]. Unlike genetic mutations, epigenetic marks are potentially reversible. Therefore, epigenetic approaches for prevention and treatment, such as nutritional supplementation and/or pharmaceutical therapies, may be developed to counteract negative epigenomic profiles.

Emerging evidence suggests that epigenetic reprogramming of BDNF by chronic cocaine intake may not only alter neuronal and behavioral phenotype in the cocaine-addicted male rats but also could be transmitted to their next generation [58]. While adverse environmental conditions may reduce BDNF expression through repressive histone H3 methylation at the BDNF promoters in rodent brains [52,59,60]. In contrast, environmental enrichment has been shown to produce opposite changes, significantly increasing hippocampal BDNF expression through complex histone remodeling at its promoters [61]. In turn, an exercise regimen known for its capacity to enhance learning and memory has recently been shown to promote remodeling of chromatin containing the *Bdnf* gene, in conjunction with elevation of levels of p-Ca^{2+}/calmodulin-dependent protein kinases II (CaMKII) and p- cAMP response element-binding protein (CREB) molecules intimately involved in the pathways by which neural activity engage mechanisms of epigenetic regulation to stimulate *Bdnf* transcription

[62]. The results of these studies emphasize the influence of metabolic signals on the epigenome and their capacity to alter feeding behavior. The fact that exercise and BDNF have been associated with reducing depression and promoting cognitive enhancement implies the fascinating possibility that epigenetic regulation of the *Bdnf* gene can be a biological mechanism by which exercise can promote mental health and build resistance to neurological disorders. The original concept of epigenetics implies the idea that modifications in DNA expression and function can contribute to inheritance of information. Some of these ideas have lately received partial support such as the negative impact of early stress on behavioral responses across generations and on the regulation of DNA methylation in the germline [63]. Similarly, a recent study has shown that early-life adversity can leave lasting epigenetic marks at the BDNF gene in the central nervous system [64].

Collaborative effects of diet and exercise

Feeding and exercise comprise part of the spectrum through which the environment has been instrumental in shaping the modern brain over thousands of years of evolution. Experimental studies in rodents have shown that exercise works in complementation with a DHA-rich diet to influence molecular systems underlying cognitive function [65]. A possible mechanism for this complementary action of exercise is exerted via restoring membrane homeostasis after traumatic brain injury (TBI), which is necessary for supporting synaptic plasticity and cognition [66]. The combined effects of a flavonoid-enriched diet and exercise potentiate the elevation of genes that are generally benevolent for neuronal plasticity and health while decreasing genes involved with deleterious processes such as inflammation and cell death [67]. Exercise has also proven to be effective in reducing the effects of unhealthy diets, i.e., counteracting the decline in hippocampal BDNF-mediated synaptic plasticity and in spatial learning skills of rats exposed to saturated fats [68]. Exercise, similar to diet, activates multiple hippocampal proteins associated with energy metabolism and synaptic plasticity [69], such as BDNF [70,71] in conjunction with other factors such as insulin growth factor-1 (IGF-1). Exercise enhances learning and memory under a variety of conditions, such that in humans, it can attenuate the mental decline associated with aging [72] and enhance the mental capacity of juveniles [73]. Blocking the action of BDNF during voluntary exercise decreases the effects of exercise on energy metabolic molecules such as adenosine monophosphate-activated protein kinase (AMPK), suggesting that cellular energy metabolism interacts with BDNF-mediated plasticity [71].

Conclusion and Future Directions

Dietary factors have the capacity to affect molecular and cellular processes that are fundamental for the transmission and processing of information in the brain. “Brain foods” such as omega-3 fatty acids provide structural material for plasma membranes, and other dietary components such as polyphenols provide support to selected energy metabolic events that assists specific aspects of synaptic functions (Figure 3). The homeostatic effects of diet in combination with exercise, on energy metabolism, lipid composition of neuronal membranes, etc, are crucial to maintain mental health and counteract the effects of neuronal vulnerability during times of disease or injury. Because the causes of most neurological disorders are characterized by multiple components and cannot be isolated to a single cause,

the diffuse range of actions induced by diet and exercise are suitable to target cognitive and mental illnesses.. This implies that dietary management may become a natural, non-invasive, and cost-effective therapeutic solution to maintaining a healthy brain and a strong defense system against some of the most common disorders in the world. In addition, based on current developments in the epigenetic field, it is likely that the effects of lifestyle on the brain have the capacity to influence neurological health of future generations.

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* of special interest

** of outstanding interest

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Key Points

1. The relationship between energy metabolism and synaptic plasticity is pivotal for the action of foods on the brain.
2. Omega-3 fatty acids and polyphenols play a crucial role maintaining the plasma membrane which is crucial for neuronal signaling.
3. The dual function of brain-derived neurotrophic factor (BDNF) activating neuronal metabolism and synaptic plasticity is key for processing behavior.
4. Diet and exercise can act on the epigenome altering short and long-term events that regulate brain function and plasticity.
5. The capacity of diet and exercise to influence brain health can be harnessed to protect against neurological and psychiatric disorders.

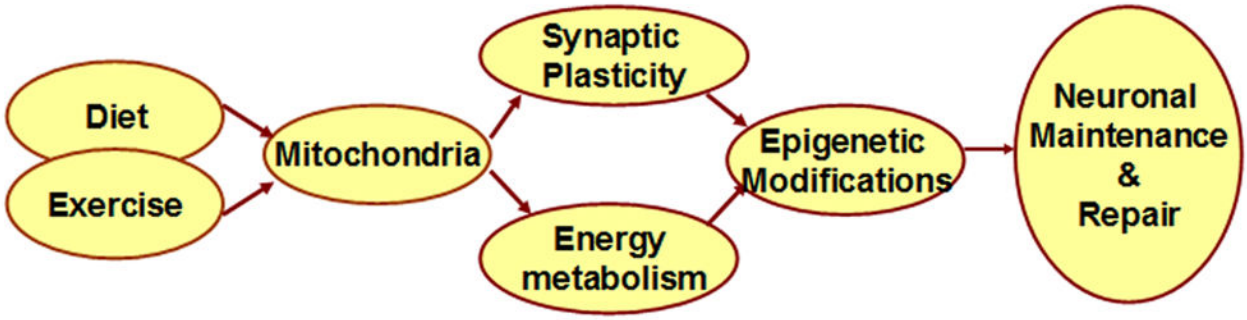

Figure 1.

Schematic representation of the actions of diet and exercise on neuronal maintenance and repair. Food and exercise can influence mitochondrial function with resulting effects on synaptic plasticity, and the neural substrates for cognition. The interaction of energy metabolism and synaptic functions is pivotal for the regulation of neuronal function and mental health, and can involve epigenetic modifications. Diet and exercise contributes to build a cognitive reserve for the brain that can be used to support neuronal function and cognition during homeostatic and challenging situations.

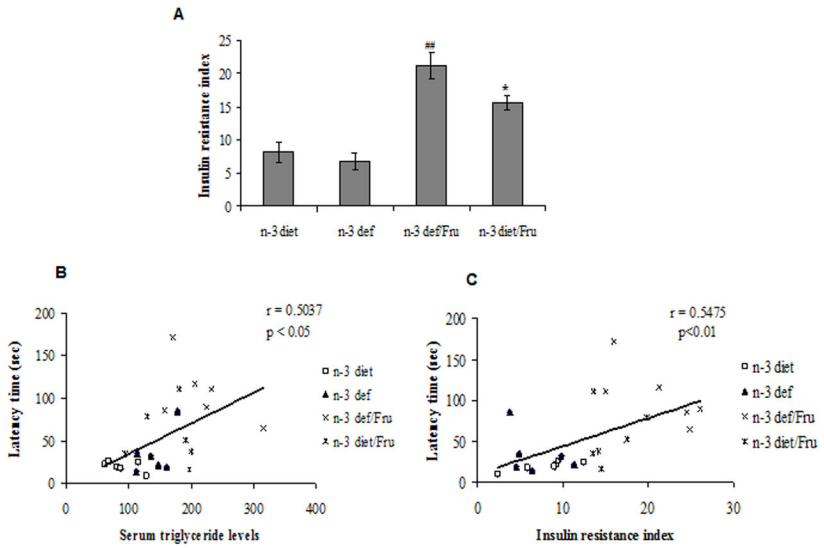

Figure 2.

(A) The metabolic syndrome can also affect the brain, and disturb energy metabolism and synaptic plasticity. The metabolic syndrome alters the signaling of insulin in nerve cells, which may disturb metabolism and plasticity. Insulin resistance index in groups subjected to n-3 and n-3 deficient diet with or without fructose water. Correlation analysis revealed a positive correlation between (B) serum triglyceride levels and latency time (C) insulin resistance index and latency time on Barnes maze. Values are expressed as mean ± SEM. $^{\#\#}P<0.01$ significant difference from n-3 diet, $^{*}P<0.05$ significant difference from n-3 def/Fru; ANOVA (one-way) followed by Newman–Keuls test. Source: Agrawal & Gomez-Pinilla, 2012 (Ref. 14).

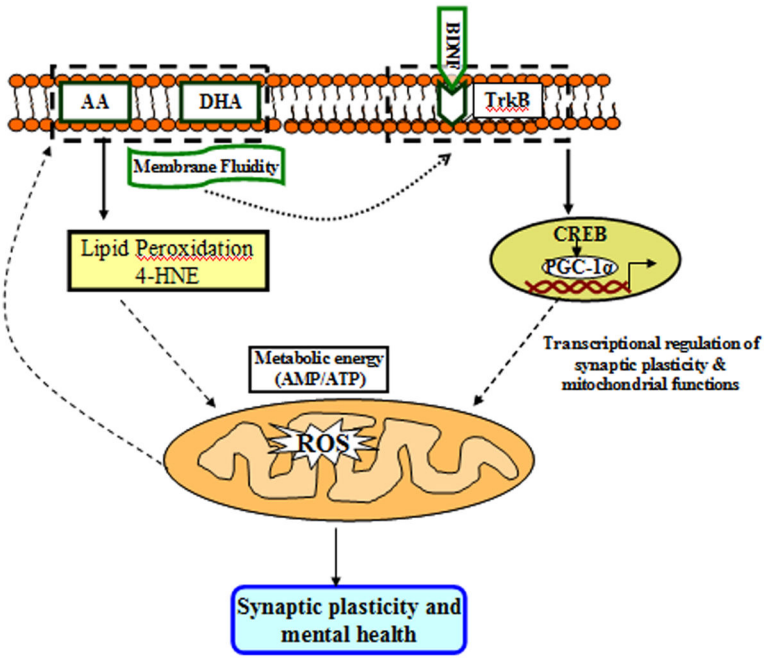

Figure 3.

Dietary factors can affect neuronal signaling and energy metabolism. The omega-3 fatty acid docosahexaenoic acid (DHA) can influence neuronal signaling by altering plasma membrane biodynamic or fluidity at synaptic regions (23, 26). DHA is essential for maintaining membrane integrity, which can affect neuronal signaling through receptors embedded in the plasma membrane., i.e., BDNF receptor TrKB activity influences the co-transcriptional regulator PGC-1α via CREB. Such signals can affect mitochondrial energy processing, thereby influencing several aspects of cellular energy metabolism and neuronal plasticity (reviewed in Ref.1). In turn, metabolic activity can also affect membrane homeostasis that supports synaptic plasticity and cognitive function (43). Excessive metabolic activity due to high caloric intake or overexertion results in production of reactive oxygen species (ROS), which promote lipid peroxidation in the cell membrane and the release of aldehydes such as 4HNE that damage cells. The homeostatic interplay between energy management in neurons and its plasticity counterparts appears crucial for the maintenance of neuronal function and neurological health.