18 Control of Fatty Acid Intake and the Role of Essential Fatty Acids in Cognitive Function and Neurological Disorders*

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18.1 INTRODUCTION
A fatty acid is a carboxylic acid often with a long unbranched aliphatic chain and is divided into two categories based on structural and chemical properties: (1) saturated and (2) unsaturated. Saturated fatty acids do not contain any double bonds or other functional groups along the chain. Unsaturated fatty acids contain at least one pair of carbon atoms linked by a double bond enabling the addition of other atoms to these carbons. Distinction between the two is simply that saturated fatty acids

* This chapter is dedicated to the memory of Dr. Sam Bhathena, an eminent scientist at the USDA, who passed away during the preparation of this manuscript.
are usually solid at room temperature whereas unsaturated fatty acids are liquid. Unsaturated fatty acids can be further divided into monounsaturated (which contains only one double bond) or polyunsaturated fatty acids (PUFAs), which contain more than one double bond. PUFAs are further grouped based either on the location of the double bonds and/or according to the chain length. An omega (ω) notation indicates the number of carbon atoms from the methyl end to the first double bond. Omega-3 (ω - 3 or n - 3) and Omega-6 (ω - 6 or n - 6) are two well-known fatty acids that are termed “essential fatty acids” (EFA). Such EFA are obtained from diet since they cannot be manufactured by cells (double bonds can be introduced into all positions of the fatty acid chain except the n - 3 and n - 6 positions). α-Linolenic acid (ALA) is an ω - 3 fatty acid that is converted to eicosapentaenoic acid (EPA) and subsequently from EPA to docosapentaenoic acid (DPA) and then to docosahexaenoic acid (DHA). Linoleic acid (LA) is the parent fatty acid for ω - 6 class of fatty acids. LA is converted to γ-linoleic acid (GLA) which through subsequent conversions results in the formation of arachidonic acid (AA) and is a precursor for several classes of eicosanoids. In the nervous system, cell membranes contain relatively high concentration of PUFAs, such as docosahexaenoic acid (DHA) (Stillwell and Wassall, 2003).

In this review we provide a synthesis of evidence concerning the neural and hormonal control on food intake with a special emphasis on long-chain fatty acids. Fatty acids act on the central nervous system (CNS) as important physiological regulators of energy metabolism and overall energy homeostasis. In addition, we will examine evidence on key neural structures and systems influenced by fatty acids that are involved in feeding behavior. Lastly, we will review evidence on the role of EFA in preventing cognitive decline as well in neurological disorders.

18.2 NEURAL AND HORMONAL REGULATION OF FATTY ACIDS

Maintenance of energy homeostasis is critical to the well-being of an individual as excess energy balance can lead to increased adiposity. A complex physiological system regulates energy intake and expenditure composed of both afferent and efferent signals to and from the brain, respectively. These signals include glucose, lipids, peptides as well as steroids, all of which influence appetite. Links between peripheral signals and the brain to regulate food intake are complex and several hypotheses including the glucostatic (Mayer, 1953, 1955, 1996) and lipostatic (Kennedy, 1953; Mayer, 1955) hypotheses have been proposed to explain their interrelationship. Based on the observation that neurons primarily use glucose, the glucostatic theory posits that food intake is determined by the use of glucose by neurons and fluctuations in glucose availability or usage are linked to food intake. If glucose availability is low, neurons would be activated and hunger increased but when the rate of glucose utilization is high, the activity of the brain cells sensitive to glucose is diminished (see Levin et al., 2004). Thus energy intake would keep up with energy expenditure and thereby maintain energy balance. A major difference between peripheral tissues, such as muscle and the brain is that the neurons cannot store glucose, indicating that the metabolism of glucose may have a unique place in the regulation of appetite. Lipostatic theory is based on the observations that neurons monitor the levels of circulating lipids which is indicative of the nutritional status and that lipid storage
in the organism is connected to the neuronal or hormonal control of appetite. Thus, according to this theory, circulating levels of hormones including leptin or insulin, as well as substrates such as fatty acids, modulate hypothalamic function in determining appetite. While both glucostatic and lipostatic theories have studies supporting their hypothesis, energy regulation is far more complex and likely both mechanisms influence each other in the CNS to regulate overall energy homeostasis.

Investigations into the neural control of energy balance began with studies that showed lesions of specific nuclei in the hypothalamus could either produce increased or decreased food intake in animals depending on the location of the lesion (Anand and Brobeck, 1951; Stellar, 1954). In addition to the hypothalamus, other centers in the brain that contribute to appetite control include the brain stem (Carlisle and Reynolds, 1961), limbic structures, and the cerebral cortex (Grossman and Grossman, 1963; see Berthoud, 2002 for review). A neural network that includes these structures, with coordinated signals amongst them, likely influences energy regulation in the organism. Traditionally, adipose tissue, liver, and skeletal muscle have been the focus of such research, but the role of CNS in sensing the energy needs of the organism and conveying such information to the peripheral centers is vastly appreciated. Most research, however, centers on the role of the hypothalamus. The hypothalamus in the brain contains nuclei that control energy homeostasis as well as the regulation of food intake generally by altering the expression of neurotransmitters or neuromodulators (Kalra et al., 1999). The arcuate nucleus (ARC), which is located around the base of the third ventricle, responds to circulating levels of leptin, ghrelin, and insulin. The ARC, surprisingly, is not protected by the blood–brain barrier (BBB) (Brightman and Boradwell, 1976) but not all circulating hormones cross the BBB freely to influence the ARC (Banks et al., 1996; Banks, 2004) indicating a likely regulatory mechanism at the BBB. Two major nuclei in the ARC that play important roles in feeding are (1) the ventromedial nucleus of the ARC that contains the orexigenic (feeding promoting) center and expresses neuropeptides agouti-related protein (AgRP) and neuropeptide Y (NPY) (Broberger et al., 1998; Hahn et al., 1998) (2) ventrolateral nucleus of the ARC contains cells that are anorexigenic (feeding inhibitors) and expresses proopiomelanocortin (POMC)/alpha-melanocytestimulating hormone (a-MSH) and cocaine- and amphetamine-regulated transcript (CART; Elias et al., 1998; Kristensen et al., 1998). Melanocortin receptors, receptors for MSH, and adrenocorticotropic hormone (ACTH), are a subfamily of G protein-coupled receptors (Adan and Gispen, 1997) that consist of at least five subtypes. a-MSH secreted from POMC/CART neurons acts on melanocortin 3/4 receptors in the hypothalamus, whereas AgRP secreted from NPY/AgRP neurons acts on these receptors as an antagonist. Thus, melanocortin 3/4 receptors in the hypothalamic neurons play an integral role in the central control of appetite and energy expenditure.

Extensive reciprocal connections exist between the hypothalamus and the brainstem, particularly the nucleus of the solitary tract (NTS) (Ricardo and Koh, 1978). The NTS lies in close proximity to area postrema, which benefits from some lack of the BBB, and thus may be influenced by circulating levels of hormones or fatty acid metabolites. NTS has a high density of NPY-binding sites (Harfstrand et al., 1986) and NPY-expressing neurons (Sawchenko et al., 1985). In addition, melanocortin four receptors are also expressed in the brainstem (Mountjoy et al., 1994).
The corticolimbic structures play an important role in appetite regulation likely by modulating reward, cognitive, and emotional factors. Using functional magnetic resonance imaging (fMRI) to investigate activation of reward system in the brain, Stoeckel et al. (2008) reported that pictures of high-calorie foods produced significantly greater activation in the cortex, hippocampus, and striatum of obese subjects when compared to controls. Neurobiological responses in obese subjects to an implantable gastric stimulator (IGS), which induces stomach expansion via electrical stimulation of the vagus nerve, showed increased metabolism in the hippocampus as assessed by positron emission tomography and 2-deoxy-2\(^{18}\)F-fluoro-D-glucose (Wang et al., 2006), indicating the importance of the hippocampus in modulating eating behaviors linked to emotional eating. A recent study indicated that in rodents, gastric electric stimulation may increase the expression of cholecystokinin (CCK), a hormone, in the hippocampus (Xu et al., 2008) and thus may be involved in inhibiting food intake. In addition, CART, POMC, NPY, and AgRP mRNAs are all expressed in the adult human hippocampus (Bai et al., 2005) as well as in rat hippocampus (Bai et al., 2005 and references therein), but their role in regulating appetite is not clear.

Numerous hormones play a key role in appetite regulation generally through their action on neural centers. Adipocytes, the gastrointestinal tract, and the pancreas are some of the major sites of hormone production in the periphery. One of the first hormones from the periphery implicated in the regulation of metabolism is CCK (see Beglinger, 2002, for review). CCK acts on the peripheral vagal afferent receptors to inhibit food intake, through its eventual actions on the brainstem. As mentioned above, CCK may also exert its effects on the hippocampus.

Leptin, an endocrine hormone and a product of ob gene, is secreted predominantly by adipocytes and acts on the hypothalamus. Leptin reduces adiposity and is another example of the endocrine-brain signaling pathway that regulates food intake. In the CNS, leptin acts to suppress appetite and increase energy metabolism (Halaas et al., 1995; Pelleymonter et al., 1995). Leptin administered peripherally (Pelleymonter et al., 1995; Hwa et al., 1997) or centrally (Hwa et al., 1996) to ob/ob mice reduces appetite, decreases fat mass, and increases metabolic rate. In the CNS, leptin receptors in the hypothalamus (Tartaglia et al., 1995) are hypothesized to mediate satiety by decreasing NPY levels (Campfield et al., 1995; Stephens et al., 1995) and/or by increasing metabolism through activation of the efferent sympathetic system (Campfield et al., 1996a,b). In the periphery, the mechanism of action of leptin, as studied in cell cultures and isolated tissue, is postulated to be through its effects on increasing metabolism primarily by intracellular lipolysis and fatty acid metabolism (Koyama et al., 1997; Shimabukuro et al., 1997).

Insulin is an important hormone that regulates food intake. Insulin is produced by the pancreas. Levels of insulin vary with adiposity (Bagdade et al., 1967). Central administration of insulin decreases food intake in primates (Woods et al., 1979) as well as in rats (Ikeda et al., 1986; Menendez and Atrens, 1991) and hypothalamus is implicated in insulin's action in reducing food intake (Strubbe and Mein, 1977; Menendez and Atrens, 1991).

Ghrelin is an orexigenic factor that is released from the stomach, duodenum, and ileum (Kojima et al., 1999; Date et al., 2000), and plasma ghrelin levels are inversely correlated with body mass index, a measure of obesity (Otto et al., 2001). Central
or peripheral administration of ghrelin increases food intake and body weight in rats (Tschop et al., 2000; Wren et al., 2001b). Intravenous administration of ghrelin to healthy human subjects also stimulates food intake (Wren et al., 2001a). Ghrelin is hypothesized to exert its action on the ARC in the rat hypothalamus (Tamura et al., 2002). Other hormones secreted by endocrine glands also affect energy balance including thyroid hormones, corticosterone, and growth hormones (see Kalra et al., 1999; Coll et al., 2007 for reviews). The exact mechanism by which such hormones act, whether alone or in concert, to regulate food intake is not clear.

Another class of molecules that also influence appetite is members of the fatty acid biosynthetic pathway including malonyl-CoA, an intermediate of fatty acid biosynthesis. Fatty acid oxidation plays a key role in the control of food intake. Evidence indicates an important role of fatty acids in the CNS where it plays a key role in physiological regulation of glucose metabolism and general energy homeostasis (Seeley and Woods, 2003; Lam et al., 2005a,b). Increased feeding by inhibition of fatty acid inhibition is hypothesized to send signals to the brain by vagal afferents. The brain plays an important role in the evaluation of energy status because the hypothalamus is the principal site that integrates signals from the periphery and other brain areas to regulate feeding behavior. The hypothalamus plays an important role in monitoring fatty acid metabolism as part of its energy-sensing function (Kim et al., 2002; Mobbs and Makimura, 2002; Obici et al., 2003). Fatty acids can be imported into the cell either from the blood circulation or synthesized de novo inside the cell. Within the cell, fatty acids either undergo oxidation in the mitochondria for energy production or may be directed towards glycerolipid synthesis (triglycerides or phospholipids) for later energy production or membrane function. In lipogenic tissues including liver and adipose, the fatty acid pathway is generally involved in the storage of excess energy in the form of triglycerides which can subsequently be oxidized to provide energy. Intracellularly, acetyl-CoA is the precursor for de novo synthesis of fatty acids. Acetyl-CoA carboxylase (ACC) catalyzes the conversion of acetyl-CoA to malonyl-CoA which is the basic unit for fatty acid synthesis by the enzyme fatty acid synthase (FAS) in the cytosol. To undergo mitochondrial oxidation, however, fatty acids must cross both the outer and inner mitochondrial membranes. This process is catalyzed by carnitine palmitoyltransferase-1 (CPT-1) which is bound to the outer mitochondrial membrane and subsequently by carnitine palmitoyltransferase-2 (CPT-2), an inner mitochondrial membrane enzyme. Two isoforms of ACC exist (ACC1 and ACC2) (Bianchi et al., 1990) with divergent functions for each and both isoforms are regulated by phosphorylation by 5'-adenosine monophosphate-activated kinase (AMPK), an energy-sensing enzyme. ACC1 (also known as ACC-α) catalyzes the carboxylation of acetyl-CoA to form malonyl-CoA. On the other hand, ACC2 (also known as ACC-β) colocalizes with CPT-1 and regulates mitochondrial fatty acid oxidation. Interestingly, malonyl-CoA is a potent inhibitor of CPT-1 (Ruderman et al., 2003) and has effects on both fatty acid oxidation in the mitochondria as well as the synthesis of various lipids. Disturbances in malonyl-CoA regulation may contribute to insulin resistance (Ruderman et al., 1999) and obesity (Ruderman et al., 1999; Loftus et al., 2000). ACC2-deficient mice accumulate less malonyl-CoA and show significant reduction in fat in adipose tissue, despite increased food intake, indicating that they were expending energy at an increased rate (Abu-Elheiga et al.,
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2003). ACC has been detected in select neurons of the brain, notably in the ARC of the hypothalamus (McGarry and Brown, 1997), although which ACC isoforms are present in these neurons, however, is not clear. ACC has also been detected in other brain cell types including astrocytes in culture (Blazquez et al., 1998) and oligodendrocytes (Spencer et al., 1993), but the relative contribution of each cell type to food intake is currently not known. Hypothalamic inhibition of CPT-1 decreases food intake and suppresses endogenous glucose production (Ruderman et al., 1999).

One important enzyme that plays a key role in cellular energy homeostasis, as mentioned previously, is AMPK (Hardie and Hawley, 2001). AMPK is an energy-sensing kinase, which responds to changes in the energy levels of the cell and the whole body in order to maintain adequate adenosine triphosphate (ATP) levels in the cell. AMPK phosphorylates and inactivates ACC, thereby inhibiting fatty acid synthesis by decreasing malonyl-CoA availability (Frederich and Balschi, 2002). AMPK immunostaining in mouse brain sections reveals a predominantly neuronal distribution although it is also detected in activated astrocytes (Turnley et al., 1999). Significant interactions exist between fatty acids and the endocrine system (Bhathena, 2000, 2006). Hypothalamic malonyl-CoA responds to the level of circulating glucose and leptin, both of which affect energy homeostasis (Wolfgang et al., 2007). Leptin decreases AMPK activity in the hypothalamus (Minokoshi et al., 2004). Intracerebroventricular (ICV) injection of leptin, concomitant with inhibiting AMPK, activates ACC, the key regulatory enzyme in fatty acid biosynthesis, in the ARC and paraventricular nucleus (PVN) in the hypothalamus indicating that hypothalamic ACC activation makes an important contribution to leptin's anorectic effects (Gao et al., 2007). Orexigenic hormones such as ghrelin and cannabinoids stimulate hypothalamic AMPK leading to an increase in appetite while inhibiting AMPK activity in the liver and adipose tissue, thereby leading to lipogenic effects (van Thuijl et al., 2008).

Pharmacological modulation of fatty acid metabolism has been utilized to inhibit food intake (Loftus et al., 2000). C75 (trans-4-carboxy-5-octyl-3-methylenebutyrolactone), originally designed as a FAS inhibitor (Kuhajda et al., 2000), causes profound, reversible weight loss in lean mice, diet-induced obese (DIO) mice, leptin-deficient (ob/ob) mice (Loftus et al., 2000; Thupari et al., 2004), and normal lean rats (Loftus et al., 2000). FAS inhibitors were initially developed as inhibitors of tumor progression, but these inhibitors also produced weight loss in mice (Loftus et al., 2000). ICV administration of C75 also rapidly suppresses food intake (Clegg et al., 2002; Aja et al., 2008). When administered peripherally, C75 decreases NPY/AgRP levels (Loftus et al., 2000) and increases POMC/CART levels in the brain (Thupari et al., 2004; Tu et al., 2005). In addition, ICV administration of ghrelin in mice blocks the inhibitor effects of C75 and decreases NPY levels and increases POMC/CART levels (Hu et al., 2005) indicating the interrelationship that exists between FAS inhibition and these neuropeptides. However, multiple distinct events related to fatty acid metabolism in the CNS coordinate energy balance as glucose, insulin, amino acids, leptin, and other metabolites all regulate FAS directly or indirectly (Semenkovich et al., 1993; Dudek and Semenkovich, 1995; Fukuda et al., 1999). One example is the recent report by Chakravarthy et al. (2007) who used a FAS knockout mouse with a genetic inactivation of FAS in the hypothalamus and pancreatic β cell. While these mice had less adiposity and decreased food intake (similar to what is
observed with C75-treated animals), administration of a peroxisome proliferator-activated receptor-α (PPARα) agonist into the hypothalamus increased PPARα target genes and normalized food intake. This is novel since PPARα is a transcription factor that is believed to respond to starvation, but is regulated by FAS, an enzyme that is activated by feeding. Such complexity only further highlights increased modulation that exists intracellularly in the fatty acid metabolic pathway in the brain to maintain energy balance. Figure 18.1 shows the interaction of some hormonal and neural pathways in the control of food intake.

Cellular mechanisms by which fatty acids regulate neuronal activity are not clear, although their actions on ion channels in neurons as well as other cell types have been reported. Witt and Nielsen (2004) reported an increase in [3H]Diazepam-binding in rat cortex in vitro upon treatment with fatty acids indicating an influence on the γ-aminobutyric acid (GABA)/benzodiazepine receptor/Cl⁻ ion channel. Their effect on G protein-gated K⁺ channels by antagonizing the ATP-dependent gating

![Figure 18.1](image-url)
in neurons and cardiac myocytes has also been reported (Kim and Pleumsamran, 2000). In gastric myocytes fatty acids markedly increase $I_{Kcaw}$, a calcium-dependent potassium current, and the enhancing potencies were related to the number of double bonds in the fatty acid chain (Zheng et al., 2005). Hyperpolarization of rodent hepatocytes by palmitate has also been reported (Rossi and Scharrer, 1995; Rossi et al., 1995). Whether these mechanisms occur in the brain in the hypothalamus or in other neural centers that are involved in the regulation of food intake is not known.

Sensitivity to EFA is observed in the periphery in the control of obesity. As a percentage of total fatty acids, $\alpha - 3$ EFA in liver and adipose tissue lipids were significantly lower in the obese mice than in the lean controls (Cunnane et al., 1985). Obese subjects have low EFA content in their circulating plasma lipids when compared to nonobese controls (Rössner et al., 1989). Serum and hepatic AA levels were elevated in obese compared to lean rats indicating abnormal arachidonate distribution in the obese Zucker rat (Phinney et al., 1993). A recent study reported that GLA reduced weight regain in humans following major weight loss (Schirmer and Phinney, 2007). While mechanisms underlying the effects of EFA in reducing obesity are not clear, LA significantly decreases adiponectin and leptin secretion, two adipokines known to influence weight gain and insulin sensitivity, in insulin-stimulated primary rat adipocytes (Pérez-Matute et al., 2007). Whether such a phenomenon occurs in the brain as well is not yet known.

### 18.3 ROLE OF FATTY ACIDS IN COGNITION

About 50%-60% of the dry weight of the brain consists of lipids and PUFAs constitute approximately 30% of the lipid content (Sastry, 1985). $\alpha - 3$ fatty acids including EPA and DHA play important roles in the development and maintenance of normal CNS structure and function. Chronic dietary intake of essential PUFAs may modulate learning and memory by being incorporated into neuronal plasma membranes. Representatives of two PUFA families, the $\alpha - 3$ and $\alpha - 6$ types become integrated into membrane phospholipids, where the actual ($\alpha - 6)/(\alpha - 3$) ratio is hypothesized to determine membrane fluidity and thus the function of membrane-bound proteins. Animal studies suggest that a deficiency of $\alpha - 3$ fatty acids may lead to behavioral or cognitive deficits (Bourre et al., 1989; Yehuda et al., 1999; Hichami et al., 2007). In addition, supplementation of DHA enhances cognitive function in both adult and old mice (Shirai and Suzuki, 2004). This study also reported an enhancement when DHA was supplemented with catechin, a dietary polyphenol. Whether polyphenols and $\alpha - 3$ fatty acids act at multiple independent sites to improve cognition is not known and should be investigated further. While DHA has beneficial effects, an increase in lipid peroxides formation is also a possibility (Halliwell, 1992) which may result in oxidative stress that could be harmful to normal brain (Yavin et al., 2002). Dietary sources especially rich in $\alpha - 3$ fatty acids include fish such as tuna, trout, and salmon as well as some plant oils which are a rich source of ALA.

DHA is a key component of neural and retinal membranes, and rapidly accumulates in the brain during gestation and the postnatal period. Long-chain $\alpha - 3$ fatty acids are thought to be important for fetal neurodevelopment. Positive associations
have been shown between maternal intake of fish, seafood, and ω – 3 fatty acids during pregnancy and/or lactation and visual and cognitive development in human studies. Higher cord DHA concentration was associated with longer gestation, better visual acuity, and novelty preference on the Fagan Test at 6 months, and better Bayley Scale mental and psychomotor performance at 11 months. By contrast, DHA from breast-feeding was not related to any indicator of cognitive or motor development in this full-term sample (Jacobson et al., 2008). Despite encouraging results in human intervention studies (Oken et al., 2008; Olsen et al., 2008; Strain et al., 2008), several studies were unable to demonstrate a positive effect of prenatal ω – 3 supplementation (see Hadders-Algra, 2008 for review). Thus, limited evidence exists to support the notion that prenatal ω – 3 supplementation favors developmental outcome. Likewise, evidence for benefits of n – 3 long-chain PUFA on cognitive development in healthy children older than 2 years of age is too limited to allow a clear conclusion (Eilander et al., 2007). In adults, fatty fish and marine ω – 3 PUFA consumption was associated with a reduced risk of impaired cognitive function in a middle-aged population (Kalmijn et al., 2004). There was little evidence that the ω – 3 PUFAs were associated with cognitive change in an older population aged 65+ in the absence of any neurological disorder (Morris et al., 2005).

18.4 FATTY ACIDS IN NEUROLOGICAL DISORDERS

Deficiencies in ω – 3 fatty acids or an imbalance in the ratio of ω – 3 to ω – 6 fatty acids have been implicated in a variety of neurological disorders including Alzheimer’s disease (AD), Parkinson’s disease (PD), Huntington’s disease (HD), ischemic brain injury/stroke, and multiple sclerosis (MS) as well as psychiatric disorders. Neurons lack the enzymes for de novo synthesis of DHA and AA (Hardy and Higgins, 1992) and hence they are obtained from dietary sources or synthesized mainly in the liver from the dietary precursors ALA and LA. However, astrocytes produce DHA (Moore et al., 1991) some of which is likely exported to neurons although the mechanism by which fatty acids cross the plasma membrane to enter cells is not clear. A significant portion of studies have examined the role of DHA in neurological disorders.

18.4.1 ALZHEIMER’S DISEASE

AD is an irreversible progressive neurodegenerative disorder that is the most common cause of dementia in the elderly. AD is characterized by cognitive and memory dysfunction. Neuropathologically, it is characterized by the deposition of extracellular amyloid beta (Aβ) protein and intracellular neurofibrillary tangles in the hippocampus and cerebral cortex (Khachaturian, 1985; Mirra et al., 1991). Associated synapse loss and neuronal death are key features of AD pathology. While the cause of sporadic AD is not known and is very likely multifactorial, AD is associated with several molecular and biochemical abnormalities including impaired energy metabolism/mitochondrial function and oxidative stress that may contribute to neuronal loss/dysfunction (Haass and Selkoe, 1993). More recently obesity has been recognized as an important risk factor for developing AD (Gustafson et al., 2003).
Reduced intake of ω-3 or DHA deficiency has been reported as a risk factor for AD (Soderberg et al., 1991; Conquer et al., 2000; Tully et al., 2003; Pomponi and Pomponi, 2008). But no significant difference in the proportion of fatty acids, including those of the n-6 and n-3 series, in either the grey or the white matter, were observed in any of the regions studied in AD brain compared to controls (Skinner et al., 1993). Nevertheless, dietary DHA attenuates Aβ production, AD-like neuropathological changes as well as cognitive deficits in a transgenic mouse model of AD (Hashimoto et al., 2002, 2005) or in rats infused with Aβ (Hashimoto et al., 2006). In a similar transgenic mouse model of AD, safflower oil-induced ω-3 deficiency induced apoptotic-like cell death in the brain and this was partly protected by dietary supplementation with DHA (Calon et al., 2005). A protective role of DHA in AD transgenic mice has also been reported in other studies (Lim et al., 2005; Ma et al., 2007). However, Arendash et al. (2007) reported no improvement in AD-like neuropathology or cognition in transgenic mice when treated long term on diet rich in ω-3. Whether the negative result was a consequence of assessing pathology as well as cognitive function at an advanced age as reported in this study is not known. If such is the case, however, then it is possible that the beneficial effects of DHA on cognition might be observed at an early stage of AD rather than when the symptoms of AD have advanced considerably. Gillette Guyonnet et al. (2007) reviewed 15 prospective cohort studies that focused on whether the risk of AD during aging is associated with low intake of total dietary fat, fish, and/or ω-3 fatty acids from fish. While they concluded that there was no significant association between risk of AD and ω-3 fatty acid or fish intake in some studies, a protective effect of higher fish and/or DHA intake on risk of AD was observed in others. A conclusive potential benefit of fish intake and/or DHA in reducing the risk of developing AD cannot be drawn at present.

18.4.2 Parkinson’s Disease

PD is a progressive neurodegenerative disease that is caused by the loss of dopaminergic neurons in the basal ganglia. PD is characterized clinically by muscle rigidity, tremor, a slowing of physical movement (bradykinesia) and, in extreme cases, a loss of physical movement (akinesia). Cognitive dysfunction, subtle language problems, and depression are also observed.

In an animal model of Parkinsonism, mice fed on ω-3 diet for 2–12 months showed a significant protection in preventing decline of dopamine and dopamine transporter mRNA levels when compared to controls, in response to 1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that produces symptoms resembling PD (Bousquet et al., 2008). A common treatment for PD patients is the administration of levodopa, which increases dopamine levels in the brain but can also cause unwanted dyskinesia with prolonged treatment. Pretreatment with DHA significantly reduced levodopa-induced dyskinesia without altering the antiparkinsonian effect of levodopa in a nonhuman primate model of PD (Samadi et al., 2006). In a prospective population-based cohort study of people aged ≥55, the association between intake of unsaturated fatty acids and the risk of incident PD was evaluated (de Lau et al., 2005). Intakes of total fat, monounsaturated fatty acids (MUFAs),
and PUFAs, were significantly associated with a lower risk of PD. A double-blind, placebo-controlled study showed that PD patients taking fish oil, with or without antidepressants, reduced depressive symptoms indicating that the intake of ω-3 had an antidepressant effect or acted as adjuvant therapy with some other medication for PD (da Silva et al., 2008). However, more studies are needed to evaluate thoroughly the beneficial effects of ω-3 in PD.

18.4.3 HUNTINGTON’S DISEASE

HD also called Huntington’s chorea is a progressive inherited neurodegenerative disease characterized by abnormal body movements and a lack of coordination (Harper, 1996). It is one of several polyglutamine-related diseases caused by a trinucleotide repeat expansion of Huntingtin gene. The disease is characterized by a profound neuronal degeneration in the striatum with some additional atrophy of the frontal and temporal cortex. The most common symptoms are jerky, random, and uncontrollable movements called chorea, although very slow movement and stiffness (bradykinesia, dystonia) sometimes appear instead or in later stages.

Early and sustained administration of EFA as a mixture of EPA, DHA, and LA to transgenic HD mice (R6/1 mice) protects against motor deficits when compared to placebo (Clifford et al., 2002). In a randomized, placebo-controlled, double-blind trial of highly unsaturated fatty acid therapy, HD patients showed a significant improvement in Dyskinesia Rating Scale (Vaddadi et al., 2002; see Das and Vaddadi, 2004 for review).

18.4.4 ISCHEMIA/STROKE

Stroke is caused by an interruption of the blood flow to any part of the brain. It can be classified into two major categories: ischemic and hemorrhagic. Ischemia stroke is due to interruption of the blood supply due to blood clot, while hemorrhagic stroke is due to rupture of a blood vessel or an abnormal vascular structure. Stroke can lead to vascular leakage, inflammation, tissue injury, and necrosis. Long-term outcome of stroke depends on the region of the brain that is affected and the severity and generally paralysis, cognitive deficits, and speech and language problems may occur in survivors. Some major risk factors for stroke include age, obesity, diabetes, hypertension, high cholesterol, and poor diet.

Rats fed on ω-3 diet for 6 weeks prior to middle cerebral artery occlusion show reduced ischemic damage compared to controls (Relton et al., 1993). Later studies have also shown protective effects of fish ω-3 in animal models of ischemia (Bas et al., 2007; Ozen et al., 2008). ALA and DHA exert significant neuroprotective effects in animal models of focal or global ischemia (Lauritzen et al., 2000; Heurteaux et al., 2006). LA also prevents both necrosis and apoptosis of motor neurons in spinal cord ischemia in rats (Lang-Lazdunski et al., 2003). Chronic administration of DHA prior to inducing forebrain ischemia ameliorated spatial cognitive deficits in rats (Okada et al., 1996).

Administration of highly purified EPA reduced the risk of recurrent stroke in a Japanese population of hypercholesterolemic patients receiving low-dose statin
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therapy (Tanaka et al., 2008). A prospective cohort study of women reported that higher consumption of fish and ω-3 PUFAs reduced risk of total stroke and thrombotic infarction, but not the risk of hemorrhagic stroke (Iso et al., 2001). A population-based cohort from a community intervention program in Sweden, however, reported that increased levels of EPA and DHA did not decrease the risk for stroke (Wennberg et al., 2007). Balancing the risks and benefits of adequate fish consumption with the relative risk of toxic environmental contaminants in the fish should be considered (Domingo, 2007; Domingo et al., 2007a,b). Nevertheless, ω-3 fatty acids appear to have a beneficial effect in preventing neural damage in ischemia/stroke.

18.4.5 MULTIPLE SCLEROSIS

MS is an autoimmune condition in which the immune system attacks the CNS leading to demyelination of neurons. MS affects white matter in the brain and spinal cord. More specifically, MS destroys oligodendrocytes that form the myelin sheath around the axons of neurons, to help the neurons conduct electrical signals. MS results in a thinning or complete loss of myelin that results in the inability of neurons to conduct electrical signals effectively. Symptoms include muscle weakness, abnormal muscle spasms, difficulties with coordination and balance (ataxia), swallowing (dysphagia), acute or chronic pain syndrome, and bladder and bowel difficulties. Cognitive impairment has also been reported.

Swank et al. (1952) initially reported a lower incidence of MS in a coastal Norwegian community which had a high intake of fish when compared to a rural community. Decreased levels of ω-3 in plasma as well as adipose tissue of MS patients have also been reported (Holman et al., 1989). Dietary supplementation of ω-3 for 6 months to MS patients resulted in significant reduction in cytokines IL-1β, IL-2, IFNγ, and TNF-α as well as prostaglandin E2 (PGE2) and leukotriene B4 in peripheral blood mononuclear cells (Gallai et al., 1995; Calder, 1997). Reduced production of these proinflammatory eicosanoids and the decrease of some cytokines may underlie some of the beneficial actions of ω-3 in MS.

Mechanisms underlying the neuroprotective effects of EFA are not clear. Antiapoptotic (Wu et al., 2007), neurotrophic (Rapoport et al., 2007), antioxidant (Packer et al., 1997), and anti-inflammatory effects (Das, 2007) have all been suggested as potential mechanisms based on in vitro or animal studies. In addition, regulation and normalization of intracellular Ca²⁺ by DHA in neural cultures has been reported (Sergeeva et al., 2005). Likely more than one pathway is involved, and possibly cross talk with other signaling pathways is also part of its protective action.

18.5 SUMMARY AND PERSPECTIVES

Obesity is a global health problem with nearly 1 billion people categorized as obese. It is estimated that in the United States ~60% of the adult population and nearly 13% of children are obese or overweight. Obesity is often associated with, or considered a major risk factor for diabetes, cardiovascular diseases, stroke, and cancer, but now it is also recognized as a risk factor for AD, a progressive neurodegenerative disease.
Obesity is also associated with declined cognitive function. Neural regulation of food intake is not only involved in behavior related to appetite but also in sensing the energy needs of the organism. The CNS including the hypothalamus, the brain stem, and the limbic system, with the help of autonomic nervous system, is sensitive to levels of metabolic and endocrine intermediates including glucose, fatty acids, insulin, and leptin that reflect peripheral energy status.

Both central and peripheral signals play important roles in regulating the complicated neuronal circuitry that regulates feeding and energy homeostasis. While much research into the role of fatty acids, based on in vivo and in vitro studies, have increased our knowledge, understanding their molecular mechanisms might provide new targets to prevent or attenuate obesity. Considering that multiple neural pathways function in concert to determine food intake, a more definitive role of how all these pathways relay information to one another and how various signaling molecules interact to eventually regulate energy homeostasis should permit a better understanding of appetite regulation. Furthermore, cellular mechanisms underlying the effects of fatty acids is not clear and should be investigated further in order to understand their effects on neural cells. While most studies have investigated the role of fatty acids on neurons, their effects on other cell types in the brain including astrocytes and oligodendrocytes are sparse. This would appear to be an important area of investigation since neuronal–astrocyte interactions are critical in determining the function of neurons especially since astrocytes provide energy substrates to neurons (see Panickar and Norenberg, 2005 for review). Further studies are also needed to examine the role of reward and cognition centers in the brain that modulate food intake. In addition, the function of orexigenic and anorexigenic peptides in the hippocampus to regulate appetite is not clear and needs further investigation. There is also evidence to indicate an important role for EFA in improving cognitive function and for neuroprotective effects of such are also appreciated, but more research and definitive data are required to reach conclusive answers.

ACKNOWLEDGMENTS

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ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ACC</td>
<td>acetyl-CoA carboxylase</td>
</tr>
<tr>
<td>AD</td>
<td>Alzheimer’s disease</td>
</tr>
<tr>
<td>ALA</td>
<td>α-linolenic acid</td>
</tr>
<tr>
<td>AMPK</td>
<td>5’-adenosine monophosphate-activated protein kinase</td>
</tr>
<tr>
<td>AA</td>
<td>arachidonic acid</td>
</tr>
<tr>
<td>AgRP</td>
<td>agouti-related protein</td>
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<tr>
<td>ARC</td>
<td>arcuate nucleus</td>
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<tr>
<td>BBB</td>
<td>blood–brain barrier</td>
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<tr>
<td>CART</td>
<td>cocaine- and amphetamine-regulated transcript</td>
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<tr>
<td>CCK</td>
<td>cholecystokinin</td>
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</tbody>
</table>
Fat Detection: Taste, Texture, and Post Ingestive Effects

CNS central nervous system
CPT carnitine palmitoyltransferase
DHA docosahexanoic acid
DPA docosapentaenoic acid
EFA essential fatty acids
EPA eicosapentaenoic acid
FA fatty acids
FAS fatty acid synthase
GLA γ-linoleic acid
HD Huntington’s disease
LA linoleic acid
MS multiple sclerosis
MSH melanocyte-stimulating hormone
NPY neuropeptide Y
NTS nucleus of the solitary tract
PD Parkinson’s disease
POMC proopiomelanocortin
PUFA polyunsaturated fatty acid

REFERENCES


Control of Fatty Acid Intake and the Role of Essential Fatty Acids


Fat Detection: Taste, Texture, and Post Ingestive Effects

Control of Fatty Acid Intake and the Role of Essential Fatty Acids


