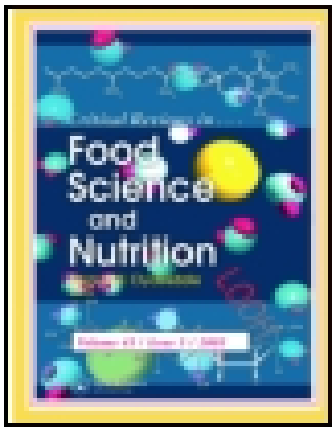

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Shlomo Yehuda[a] & Sharon Rabinovitz[ab]
[a] Psychopharmacology Lab, Department of Psychology, Bar Ilan University, Ramat Gan, Israel
[b] School of Criminology, University of Haifa, Mount Carmel, Israel
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The Role of Essential Fatty Acids in Anorexia Nervosa and in Obesity

Shlomo Yehuda[1,*], Sharon Rabinovitz[1,2]

[1]Psychopharmacology Lab, Department of Psychology, Bar Ilan University, Ramat Gan, Israel

[2]School of Criminology, University of Haifa, Mount Carmel, Israel

[*]Correspondence author: Shlomo Yehuda, Psychopharmacology Laboratory, Department of Psychology, Bar Ilan University, Ramat Gan 52900, Israel. Email: syehuda31@gmail.com

ABSTRACT

The two basic questions in food intake study are what we eat, and how much do we eat. Most research is directed toward the control of how much is eaten. This is likely the result of the increased number of individuals with eating disorders in the Western world. Feeding behavior is highly complex, and is controlled by many psychological, physiological, biochemical, and immunological factors. The aim of this review is to clarify the involvement of fatty acids in eating disorders such as anorexia and binge eating disorder. The review will describe the modified fatty acid profile observed in individuals with anorexia or binge eating disorder, and discuss on what factors fatty acids can exert beneficial effects. In addition, the differences and similarities between anorexia and binge eating disorder will be discussed. We suggest that beneficial effects of essential fatty acids on both anorexia and binge eating disorder can be explained by the stabilizing effect of those fatty acids on the neuronal membrane fluidity index.

Keywords

obesity, anorexia, essential fatty acids, omega 3, Stress, cognition, sleep, cytokines, neurotransmitters

Introduction

We must eat food to survive. Food selection and food intake are determined by physiological needs as well as psychological and behavioral (including motivational and emotional) variables. "There is no love sincerer than the love of food" However, serious and sometimes critical medical syndromes can result from excessive or deficient nutritional or food intake (overeating, malnutrition, under nutrition). Such conditions may include cardiovascular, endocrine, neurological, and psychiatric symptoms.

In addition to the biological roots of eating disorders, behavioral and personality variables are centrally involved in all types of eating disorders. There is an increasing tendency to employ psychological treatments, including cognitive behavioral therapy (CBT), interpersonal psychotherapy, and family-based psychotherapy, to patients with eating disorders. These treatments have been used with and without psychopharmacological agents. While the clinical results of CBT in the treatment of eating disorders are mixed, better CBT and behavioral modification techniques should result in better therapeutic efficacy (Brown and Keel, 2012). This paper briefly reviews fatty acids and eating behavior, and then discussed the possible relationship between them.

Fatty acids

The title of a recent paper in *Nature Neuroscience* was "Neuroscience gets Nutrition" (DiLeone, 2011). The paper examined the role of polyunsaturated fatty acids (PUFAs) in depression and altered emotional behavior. Recognition of the importance of essential fatty acids (EFAs) is also a recent finding in the area of neuroscience. The profound effects of various fatty

acids or their deficits are appreciated by a variety of disciplines, including lipid biochemistry, physiology, nutrition, psychology, psychiatry, and the neurosciences in general. Simopoulos (1999) demonstrated the historical shift from a diet with a "balanced" ratio of omega-6 and omega-3 fatty acids towards a marked and significant reduction in omega-3 fatty acid intake, and explained that the general "Western diet" of today can actually be considered an omega-3-deficient diet. There is a concern that this so-called deficiency may lead to coronary heart disease and high cancer mortality.

Linoleic acid (LA; omega-6; 18:2n6) is the parent fatty acid of the omega-6 group. LA is not synthesized by the human body, and therefore must be supplied in the diet. All other members of the omega-6 group are derivatives of LA. Similarly, the parent compound of the omega-3 group is alpha-linolenic acid (ALA, omega-3; 18:3n3). All other members of the omega-3 group are derived from ALA, and together they form the PUFAs. In each group, the derivative fatty acids can convert to longer chain fatty acids through two mechanisms: desaturation and elongation. Because the enzymes that are involved in these mechanisms have the same functions in the two fatty acid groups, the omega-6 and omega-3 fatty acids compete for the same enzymes.

While the differences between omega-6 and omega-3 fatty acids are very small (and may appear insignificant) from a chemical point of view, they exert different and sometimes even opposite biological effects. These opposing effects are not easily explained. It was recently suggested (Feller et al., 2002) that the distinction between omega-6 and omega-3 PUFAs is based on the differential capacity of proteins, and of large and membrane-bound proteins in particular, to recognize various PUFAs.

The importance of the ratio of omega-6 to omega-3 fatty acids

There are several aspects to the issue of the optimal recommended ratio of omega-6 fatty acids to omega-3 fatty acids. One aspect is the total daily dietary intake recommended in various phases of life (e.g., infancy, pregnancy, adulthood, and old age). Another aspect is the optimal ratio of PUFAs for dietary supplementation or medical treatment of specific conditions. PUFAs are used in the body in a variety of conditions, including dermatological diseases and cardiovascular disorders. One particular area of interest is the role of PUFAs in the brain and the utility of PUFAs for the protection and stabilization of the neuronal membrane in health and in disease.

The effects of PUFAs on brain function can be divided into at least five categories: (1) modification of neuronal membrane fluidity, (2) modification of membrane activity-bound enzymes, (3) modification of the number and affinity of receptors, (4) modification of the function of neuronal membrane ionic channels, and (5) modification of the production of neurotransmitters and brain peptides (Yehuda et al., 2001).

Many studies have demonstrated that various PUFAs mediate, or are associated with, several aspects of brain activity, ranging from the role of EFAs in neuronal structure and function, long-term potentiation (LTP), specific brain activation, and prostaglandin activity, to their roles in neurological disorders, mental disorders, and mood control. Unfortunately, the vast majority of these studies merely test one or two specific fatty acids. There are very few solid studies that experimentally examine a wide range of ratios between omega-6 and omega-3 fatty acids. This review will summarize the areas in which studies on ratios have been performed. It

will be necessary to omit some of the most fascinating areas, such as depression, psychosis, and pain.

Essential fatty acids, the blood-brain barrier, and the brain

Because EFAs must be supplied in the diet, two major issues arise. First, are EFAs and PUFAs able to cross the blood-brain barrier (BBB)? Recently, Rapoport (2001) and Edmond (2001) discussed the complex mechanism of delivery of essential PUFAs in detail, as they progress from the blood into the brain. The involvement of the BBB is crucial during two developmental periods: infancy and aging. The human infant is born with an immature BBB, and during these periods the structure and function of the BBB are not at their optimal levels. Although there have been reports of structural changes in the BBB complex in aging and in Alzheimer's patients (de la Torre and Mussivand, 1993, Ginsberg et al., 1998), the understanding of functional changes is quite limited. Most published studies did not report changes in the rate of transport of PUFAs into the brain during aging (e.g., Strosznajder et al., 1994, Terracina et al., 1992). The important (and thus far unanswered) question is whether omega-6 and omega-3 fatty acids have different rates of transport into the brain.

The second issue regarding the BBB is the brain's ability to convert LA and ALA into the longer chain fatty acids, arachidonic acid (AA) and docosahexaenoic acid (DHA). Some researchers suspect that the immature brain of the human infant is unable to make these conversions. However, the majority of studies agree that the infant brain does have this capacity (e.g., Rapoport, 2001, Su, 2001).

Brain neurotransmitters and PUFAs

The relationships between PUFA ratios and various neurotransmitters, as described before (Yehuda et al., 1998)**,** are of special interest. It is important to note that omega-3 deficiency induces the reduction of dopamine vesicle density in the cortex (Zimmer et al., 2000), as well as malfunction of the dopaminergic mesocorticolimbic pathway (Zimmer et al., 2002). The ability to recover from the dopaminergic effects of omega-3 deficiency is age-dependent (Kodas et al., 2002, Chalon et al., 1998, Acar et al., 2003). Also, the effects of ALAs on recovery from omega-3 deficiency are dependent on spatial configuration. The *trans*-isomer of linolenic acid is inactive and if not enough *cis*-isomer is supplied, a state of omega-3 deficiency will occur (Acar et al., 2003). Some studies indicate similar effects on the serotonergic system (Farkas et al., 2002).

Membrane fluidity and myelin

Before considering the effects of PUFAs on brain-mediated functions, the effects of PUFAs on brain structural components must be elucidated. Fatty acids and lipids are major components in brain structure, and are present at very high levels in the neuronal membrane and the myelin sheaths. The neuronal membrane is composed of two lipid layers. The ratio of protein to lipids is approximately 1:1 in the neuronal membrane, while the myelin sheaths are composed of approximately 70% lipids and approximately 30% protein. The protein component is especially stable, while the lipid component has a relatively high turnover rate.

To understand the diverse functions that appear to be mediated by various PUFA and by the ratio of omega-6 to omega-3 fatty acids, we proposed previously that the membrane fluidity index is the common denominator regarding the various effects of PUFAs (Yehuda et al., 1999, Yehuda et al., 2002). Some molecules are able to change the physical state (e.g., the fluidity

index) of the membrane. For example, alcohol fluidizes the membrane, while cholesterol hardens it. There are two basic questions regarding the hypothesis that PUFAs are able to modify the neuronal membrane fluidity index; first, whether changes in the lipid component of the neuronal membrane (e.g., different ratios of various fatty acids) would lead to changes in neuronal functions, and second, whether supplementation of various fatty acids would affect the composition and function of the neuronal membrane. A number of studies have shown that EFA supplementation, under certain conditions of composition and time, does modify both membrane structure and function (as summarized in Yehuda et al., 1998).

The integrity of the myelin is of utmost importance for proper axonal function. Breakage or lesions in the myelin can lead to disintegration of many functions of the nervous system. Recent studies emphasize the major involvement of dietary EFAs in the normal functioning of myelin. Moreover, EFAs are very important in the active phase of myelin synthesis. If EFAs are unavailable or metabolically blocked during this phase, amyelination, dysmyelination or demyelanation may occur (Auestad 2000, Salvati et al., 2000). If EFA deficiency occurs during the postnatal period, a major delay in the myelination process will occur, accompanied by impaired learning, motor, vision, and auditory abnormalities (Stockard et al., 2000). It is of great interest to note that similar impairments in the myelination process and cognitive function have also been observed in rodents and humans that are iron-deficient during the postnatal period (Youdim and Yehuda, 2000). Disorders that are associated with myelin malfunction or demyelization can also occur during the adult period. One such disorder is multiple sclerosis. The rate of myelin lipid turnover is age-dependent: it is very slow during aging, resulting in a slowed rate of repairing damaged myelin in older individuals (Ando et al., 2003).

Cholesterol and fatty acids

The membrane fluidity index is dependent on two major factors: the level, composition, and percentage of PUFAs in the membrane; and the level of membrane cholesterol. An increase in the PUFA level will result in fluidization of the neuronal membrane, while an increase in cholesterol will harden the membrane. Because the membrane should be at optimal physiological gel state, cholesterol, a complex lipid, is involved in many functions in the membrane. It is well established that cholesterol decreases the membrane fluidity index, which affects the activity of ion channels and receptor functions, as well as dopamine release. Moreover, cholesterol is a key molecule in the end product of the corticotropin releasing factor/adrenocorticotropic hormone axis. Considering that steroids are cholesterol derivatives, it is of great interest to find that various fatty acids have differential effects on cholesterol metabolism. Many reliable studies confirm that the administration of omega-6 fatty acids reduces the level of cholesterol in the blood. However, omega-6 fatty acids and omega-3 fatty acids differ in their modes of action with respect to cholesterol reduction, such that omega-6 fatty acids redistribute cholesterol, while the omega-3 fatty acids actually reduce the level of cholesterol in the neuronal membrane. This may explain why an increase in the serum cholesterol level is observed in humans who consume omega-3 fatty acid supplements. It has been demonstrated that omega-3 EFAs are more effective than omega-6 EFAs at reducing cholesterol levels in macrophages, most likely due to their differential effects on acyl-coenzyme A dehydrogenase activity. However, some studies have indicated that cholesterol-esterifying enzymes that incorporate free fatty acids into cholesterol esters without the participation of coenzyme A are also present in the rat brain (Horrocks and Harder, 1983).

The mechanism by which omega-6 or omega-3 fatty acids are able to reduce cholesterol levels in the blood or the neuronal membrane remains unclear, although several hypotheses have been proposed. For example, Bourre et al. (1991) claimed that ALA controls the composition of nerve membranes, which implies an inverse relationship between ALA and cholesterol level. Salem et al. (2001) proposed that DHA controls the level of cholesterol, as well as the composition and function of the neuronal membrane. Another approach suggests that the differential effects of omega-6 or omega-3 fatty acids on cholesterol level depend on the activity of PUFAs on reduced low-density lipoprotein receptor activity (unpublished data). A negative correlation was observed between membrane cholesterol level and improvement in learning capacity. A number of studies provide support for reducing neuronal membrane cholesterol through dietary supplementation with an omega-6/omega-3 compound at a ratio of 4:1 (Yehuda et al., 1997). Such a correlation was not observed after supplementation at other ratios. It is possible that this specific ratio (4:1) optimizes the uptake of PUFAs into the brain and promotes fatty acid incorporation into the neuronal membranes, while displacing cholesterol out of the membrane. The issue of the neuronal membrane cholesterol level is very important, as the level of cholesterol (and cholesterol metabolites) in aging and Alzheimer's patients' brains is very high.

Major changes in fatty acid profile and function in the blood and brain occur in animal models and in patients with eating disorders.

Types of eating disorders

The three most common types of eating disorders are anorexia nervosa, bulimia nervosa, and binge eating disorder. Anorexia nervosa is characterized by an obsessive fear of gaining weight,

refusal to maintain a healthy body weight, and an unrealistic perception of body image. Many people with anorexia nervosa fiercely limit the quantity of food they consume and view themselves as overweight, even when they are clearly underweight. Anorexia can have damaging health effects, such as brain damage, multi-organ failure, bone loss, heart difficulties, and infertility. The risk of death is highest in individuals with this disease, and has increased in recent years (Simik, et al., 2012).

Bulimia nervosa, also known as bulimia, is characterized by repeated binge eating followed by behaviors intended to compensate for overeating, such as forced vomiting, excessive exercise, or extreme use of laxatives or diuretics. Individuals with bulimia may fear weight gain and feel severely unhappy with their body size and shape. The binge eating and purging cycle is typically performed in secret, creating feelings of shame, guilt, and lack of control. Bulimia can have injurious effects, such as gastrointestinal problems, severe hydration, and heart difficulties resulting from electrolyte imbalance.

In binge eating disorder, unlike bulimia nervosa, episodes of binge eating are not followed by compensatory behaviors, such as purging, fasting, or excessive exercise. Hence, many people with binge eating disorder may also be obese and at increased risk of developing other conditions, such as cardiovascular disease. Men and women who struggle with this disorder may also experience intense feelings of guilt, distress, and embarrassment related to binge eating, which could influence progression of the disorder.

This review will be focused on anorexia and binge eating disorder.

Obesity

Definition and characterization

Obesity has traditionally been defined as a weight at least 20% above the weight corresponding to the lowest death rate for individuals of a specific height, sex, and age (ideal weight). Twenty to forty percent over ideal weight is considered mildly obese; 40-100% over ideal weight is considered moderately obese; and 100% over ideal weight is considered severely, or morbidly, obese. More recent guidelines for obesity use a measurement known as body mass index (BMI), which is the individual's weight multiplied by 703 and then divided by twice the height in inches. A BMI of 25.9-29 is considered overweight; a BMI over 30 is considered obese. Measurements and comparisons of waist and hip circumference can also provide some information regarding risk factors associated with weight. As the higher an individual's waist-to-hip ratio, the greater their chance of developing weight-associated complications. Callipers can be used to measure skin-fold thickness to determine whether tissue is muscle (lean) or adipose tissue (fat).

Much concern has been generated about the increasing incidence of obesity among Americans. Some studies have noted an increase from 12% to 18% between 1991 and 1998. Other studies have actually estimated that a full 50% of all Americans are overweight. The World Health Organization terms obesity a worldwide epidemic, and diseases that are often associated with obesity are becoming increasingly prevalent.

Excessive weight can result in many serious, potentially life-threatening health problems, including hypertension, type II diabetes mellitus (non-insulin-dependent diabetes), increased risk of coronary disease, increased unexplained heart attack, hyperlipidemia, infertility, and a higher prevalence of colon, prostate, endometrial, and possibly breast cancer. Approximately 300,000 deaths each year are attributed to obesity.

Causes and symptoms

The mechanism for excessive weight gain is clear—more calories are consumed than the body burns, and the excess calories are stored as fat (adipose) tissue. However, the exact cause is not as clear, and likely arises from a complex combination of factors. Genetic factors significantly influence how the body regulates the appetite and the rate at which it turns food into energy (metabolic rate). Studies of adoptees confirm this relationship—the majority of adoptees followed a pattern of weight gain that more closely resembled that of their birth parents than their adoptive parents. However, a genetic predisposition to weight gain does not automatically mean that a person will be obese. Eating habits and patterns of physical activity also play a significant role in the amount of weight a person gains. Recent studies have indicated that the amount of fat in a person's diet may have a greater impact on weight than the number of calories it contains. Carbohydrates like cereals, breads, and fruits, as well as vegetables and protein (e.g., fish, lean meat, turkey breast, skim milk) are converted to fuel almost as soon as they are consumed. Most fat calories are immediately stored in fat cells, which add to the body's weight and girth as they expand and multiply. A sedentary lifestyle, particularly prevalent in affluent societies such as the United States, can contribute to weight gain. In some cases, psychological factors, such as depression and low self-esteem, may also be factors in weight gain.

The biology of anorexia

Anorexia nervosa and bulimia nervosa affect millions of people each year in the United States. Some researchers hold that these disorders arise from girls and women trying to fulfill a culturally imposed ideal body image that stresses thinness. Anorexia and bulimia have proven difficult to treat using a psychology-based treatment plan alone, and it is likely that there are

many factors contributing to these disorders. However, it is clear that there is a significant biological component that leads to the manifestation of these disorders. Biological factors include genetic factors, neurotransmitter imbalances, and hormone imbalances. Genetic factors appear to play a significant role in predisposing a person to developing an eating disorder. Abnormal neurotransmitter levels have been demonstrated in bulimic and anorexic individuals. Hormone functioning and levels are also atypical in people with eating disorders.

While most studies focus on one area, and usually on just one neurotransmitter or hormone, the different biological causes of eating disorders appear to be related to one another. Anorexia nervosa is described as a disorder in which both women and men intentionally starve themselves, losing at least 15% of their normal body weight. This self-imposed food restriction usually begins during puberty and is most common among middle-to-upper class Caucasian women, affecting 1% of the US population. Amenorrhea, the cessation of the normal menstrual cycle, is a common occurrence among anorexic women. There is also tremendous discord between actual weight and perceived body weight.

Studies have shown a tendency toward genetic predisposition for developing an eating disorder. Women and girls in a family that has a member with an eating disorder are more likely than average women to develop an eating disorder themselves.

Studies conducted primarily on the hypothalamus have linked neurotransmitter levels to these eating disorders. Specifically, the ventromedial hypothalamus and lateral hypothalamus have been shown to govern eating behavior in humans, as well as in many laboratory animals. The ventromedial hypothalamus has been called the satiety center. Stimulation of this part of the brain is correlated to a feeling of satiation and to the cessation of eating behavior. Conversely,

stimulation of the lateral hypothalamus correlates with eating behavior. When operating properly, these two areas help keep the body at a specific body weight, termed the set point. Damage to either of these regions causes the set point to be altered. Eating then reflects the new set point; if the new set point is lower than normal, sometimes an animal can literally starve itself to death (Davis, 1979).

Decreasing the level of epinephrine in the ventromedial hypothalamus of rats has been correlated with the exhibition of anorexic-type behaviors. That is, rats adopt a low rate of eating, increase their rate of activity, reduce their carbohydrate intake, and rebound with overeating.

Serotonin, norepinephrine, and dopamine are all at abnormal levels in humans with anorexia and bulimia [see below]. Experiments performed on laboratory animals have revealed that when serotonin is released into either the ventromedial hypothalamus or the lateral hypothalamus, eating behavior stops and starvation results. Conversely, if serotonin levels are reduced, then obesity occurs. The administration of norepinephrine resulted in similar outcomes. Although rats are biologically far removed from humans, there are some similarities with respect to neurotransmitter function. A study using human subjects concluded that "impaired central nervous system serotonergic responsiveness may contribute to the onset or maintenance of abnormal eating patterns in patients with bulimia nervosa (Kaye and Weltzin, 1991). These researchers linked serotonin to feelings of wellbeing and satiation. After ingesting a carbohydrate-rich diet, the body converts these sugars into tryptophan (the precursor of serotonin) through a multi-step process. Thus, it has been suggested that the binge behavior of individuals with bulimia may be in response to low serotonin levels in the brain.

Anorexic patients, on the other hand, may have overactive serotonergic response centers, leading to a need to reduce brain serotonin levels by restricting food intake (Zhu et al, 2012). Excessive levels of serotonin are correlated with a nervous, jittery feeling; self-starvation may be an attempt to rid the body of this uncomfortable feeling.

Two newly discovered hormones, orexin A and orexin B, have been connected with feeding behavior in rats. By modulating feelings of hunger and satiety, scientists can influence how much a rat eats. After the injection of these hormones into the lateral hypothalamus, rats immediately began eating eight to ten times more food than normal. Following up on this finding, researchers measured elevated hormone levels when the rat was starved. It is not yet clear whether a decrease of orexins A and B results in decreased appetites; however, there are plans to genetically engineer rats that are missing the gene needed to produce them. The hypothesis underlying this research is that drugs that mimic orexin may help anorexic patients overcome their disorder, while drugs that block orexin activity may assist in the treatment of bulimia.

One common symptom of anorexia is amenorrhea, the lack of a menstrual cycle. It appears that a result of amenhorrea is the depression of three reproductive hormones: luteinizing hormone, luteinizing hormone-releasing factor, and follicle-stimulating hormone. The levels of these hormones usually return to a normal, cyclically fluctuating pattern when weight is gained back. However, menstrual cycles do not return in some individuals, even when good nutrition is received. Permanent loss of the menstrual cycle may be related to neuroendocrine function, and particularly to hypothalamus function. The likelihood of recovery from anorexia is not good for patients who do not attain a regular menstrual cycle. A few sources have suggested that anorexic

individuals are addicted to fasting, apparently because of the chemical changes brought on by starvation. Opioids, enkephalins, and endorphins are elevated in the spinal fluid of patients with anorexia. However, it is unclear whether the starving was caused by, or was the cause of, these elevated opioid levels. Some studies have found that drugs that inhibit the functioning of these opioids cause anorexic patients to gain weight. Unusual hormones levels may also affect the I-function, causing it to portray an unhealthy body image to the self. Artificial manipulation of theses targeted hormones may help in the treatment of these eating disorders by bringing the I-function's self image back into consort with reality.

Numerous questions remain to be addressed through additional research. What is the difference between girls/women and boys/men that causes such a disparity in the rates of acquiring these disorders? Do these differences stem from biological or societal roots? Is the relationship between neurotransmitter/hormonal imbalances and eating disorders purely a one-way event? Or do the anorexic and bulimic behaviors of starving, binge eating, and purging effect the body's chemical environment? Could the relationship be a snowball effect in which chemical imbalance causes an eating disorder, which in turn causes a greater chemical imbalance? By altering the body's chemical state, can the sense of self truly be changed as well? Is this changing of personalities, which to some extent are determined by genetics, a good idea?

Animal models

Anorexia

There are several animal models for anorexia nervosa (Casper, et al., 2008, Kim, 2012). The difficulty in establishing an animal model for anorexia is that anorexia is a mixture of psychological, psychiatric, hormonal, and brain biochemical factors. The models can be

classified into those that mimic the main symptom of anorexia (restriction of food intake), and models that mimic presumed ethological factors. The three main types of models are dietary restriction, activity-based anorexia (ABA), and stress-induced anorexia.

Dietary restriction is a simple model of food restriction has three major problems. First, the restriction of food intake is involuntary. Second, this model type only partially mimics the symptoms of anorexia (e.g., cogitative decline; Kim, 2012), and does not mimic other symptoms. Second, dietary restriction might have beneficial effects on the cardiovascular, endocrine, immune, and nervous systems (Mattson and Calabrese, 2010). Mattson referred to dietary restriction as "Hormeses" (this is the term for generally favorable biological responses to a low dose of a molecule that is toxic at a higher dose). Third, sometimes dietary restriction has a paradoxical effect and induces bulimia nervosa (Kim, 2012).

ABA is the most widely used animal model for anorexia, and is considered most relevant to human anorexia nervosa (Casper, et al., 2008). This model is typically characterized by a reduction in food intake and body weight paradoxically accompanied by a progressively increased activity level. A standard ABA animal model includes simultaneous introduction of diet restriction (one meal for 60-90 min per day) and access to running wheels (21-22.5 h of access per day) to the animals in the experimental condition. Over a short period, the animals die because the amount of calories consumed fails to compensate for the energy expended by running. A typical rat initially displays a gradual rise in activity level, which is followed by a dramatic increase in activity if the experiment is allowed to continue. Moreover, as activity levels increase (e.g., more than 5,000 revolutions per day), the rats' food intake and body weight decline considerably (Routtenberg and Kuznesof, 1967, Kim, 2012).

A variety of stressors are also able to induce anorexia, including cold swimming, tail pinching, direct brain stimulation, and separation (Kim, 2012). All of these manipulations induce a marked decrease in food intake and major changes in the hormones of the hypothalamic-pituitary-adrenal (HPA) axis, as well as changes in some food consumptions peptides (Casper, et al., 2008, Kim, 2012).

The genetic animal models of eating disorders are beyond the scope of this review. Some genetic models have been used to examine the brain centers, sites, and functions of the food intake network. Another model has examined the effects of manipulation on the brain reward system (Avena and Bocarsly, 2012). Notably, the vast majority of studies using genetic models did not employ pharmacological models (e.g., d-amphetamine-induced anorexia) or nutritional models (e.g., iron deficiency-induced anorexia).

Animal models for bulimia nervosa

The animal models for bulimia nervosa are similar to those for anorexia nervosa, with additional models for sham feeding and obesity. There is no rodent model that includes postprandial vomiting (Casper, 2012).

Sensory systems and anorexia

Given that taste and smell are major factors in food selection, the small number of studies in this area is surprising.

Fat or fatty acids are not among the five basic taste types that are sensed (sweet, sour, salty, bitter, and umami). It seems odd that the human tongue contains receptors for only two of the three macronutrients that we require in our diet: sweet for carbohydrates and umami for protein. Where is the taste for fat and fatty acids located? One approach is that proteins such as

CD36 in the tongue (Degrace-Passilly, 2012) or AGFD-201 (Bartoshuk and Snyder, 2008) are responsible for fat taste. Other research locates the site of fat taste in the hypothalamus (Lam, et al., 2005) and/or the brain stem (area postrema) (Migrenne, et al., 2011). In addition, chemoreceptors for fat and fatty acids had been discovered in the gut (Scafani and Ackroff, 2012).

Lean and overweight subjects react differently to fat intake (Stewat and Keast, 2012). It has also been found that a taste described as "extremely sweet" by lean subjects was not judged sweet by overweight subjects. Persons with anorexia exhibited taste reactivity deficit (Szalay, et al., 2010) and alerted response to taste stimuli. Bartoshuk et al. (2008) suggested that damage to CD36 and AGFA201 contribute to obesity.

Smell is another major factor in food intake. Some studies observed a significant decrease in olfactory functions (e.g., decreases in odor identification, odor sensitivity, and odor detection) (Schecklmann et al., 2011). Other studies did not identify such differences. In cases in which anorexia was accompanied by dopamine deregulation, such as Parkinson's disease, attention deficit hyperactivity disorder, or schizophrenia, olfactory deficits was much more pronounced (Schecklmann, et al., 2011).

Lesions in the olfactory bulb render some rats aggressive; however, most become anorexic (Yehuda, 1976). The olfactory bulb is part of the brain reward system. Surgical ablation of the olfactory bulb inhibits some effects of cocaine (Xu, et al., 2012). Treatment with a mixture of omega-3 and omega-6 fatty acids can overcome anorexia induced by olfactory bulb ablation (our unpublished results).

The BBB and anorexia

The BBB is located between the peripheral blood system the cerebral blood system. Its main role is to protect the brain from various molecules. Several molecules that regulate dietary intake are produced in the periphery and must cross the BBB from the peripheral circulation to the brain in order to exert their effects.

Proinflammatory cytokines induce anorexia. Their ability to induce anorexia depends on their ability to cross the BBB. However, these cytokines might interfere with the normal physiological functions of the BBB. A likely mechanism in anorexia is that anorexia-inducing cytokines cross the BBB and modify its function (Banks, 2001). Omega-3 fatty acids reduce the effects of proinflammatory cytokines (Das, et al., 2003, Lave, 2010).

Iron deficiency induces anorexia (Yehuda and Mostofsky, 2004) and severely alters BBB transport of amino acids, insulin, glucose, and norepinephrine (Ben Shachar, et al., 2006). A mixture of omega-3 and omega-6 fatty acids can restore some of the disturbed functions of the BBB (Yehuda, et al., 2005).

The area postrema is a circumventricular organ that lacks a BBB. Previous studies have shown that lesions of the area postrema induce anorexia (Yehuda, 1976, Yoshiharu, et al., 2010). Some food intake factors also activate the area postrema (Kasser, et al., 1989, Potes, et al., 2010, Rowland and Richmond). Rats pre-treated with a mixture of omega-3 and omega-6 fatty acids are protected from the induction of anorexia by lesioning of the area postrema (Yehuda, et al., 1988).

Cerebral blood flow and anorexia

Studies using fMRI technique (Frank, et al, 2007) indicated a decrease in the rate of cerebral blood flow in anorexic patients (Frank, 2011). This decrease has been correlated with cognitive decline (Brooks, 2012).

An independent study showed that DHA (omega-3-rich) improves cerebral blood flow in healthy young adults. This improvement was not observed with omega-6-rich eicosapentaenoic acid (EPA). It would be interesting to study this issue in individuals with anorexia nervosa.

Brain neurotransmitters and anorexia

Brain neurotransmitters such as dopamine, serotonin, acetylcholine, and GABA have been implicated in food intake mechanisms and anorexia. Dopamine is the most widely studied neurotransmitter with respect to anorexia. Dopamine mediates both the food intake system and the rearward brain system. The evidence that dopamine is involved in anorexia includes studies showing that food restriction and weight loss enhance the release of dopamine in the limbic system in response to reward clues or rewarding substances. There is also a correlation between dopamine levels and anorexia-inducing effects in the ABA model (Avena and Bocartsly, 2012). Anorexic behaviors induced by iron deficiency and D-amphetamine are also mediated by the dopamine system (Chen, et al., 2001). A mixture of omega-3 and omega-6 fatty acids was able to restore changes in the dopamine system induced by anorexia (Yehuda and Mostofsky, 2004, Yehuda et al., 1999, Yehuda, 2002).

Peptides, protein, and anorexia

It has been estimated that there are approximately 40 compounds in the body that are involved in food intake mechanisms. We will discuss three: alpha melanocyte-stimulating hormone (α-MSH), cholecystokinin octapeptide (CCK-8), and leptin.

Alpha-MSH, a 13-amino-acid peptide, is a strong inhibitor of food intake (Dutia, et al., 2012). The anorexia-inducing effect of α-MSH increases with age (Petervari, et al., 2010). The effects of α-MSH on behavior are mediated by the dopaminergic system (Yehuda and Sheleff, 1985).

CCK-8 is an 8-amino-acid peptide that induces anorexia (MacIntoch, et al., 2001). The anorexia-inducing effects of CCK-8 appear to involve both central and peripheral mechanisms (Reideberger, et al., 2003). CCK-8 is a major factor in anorexia of aging (Morlay, 2012). A mixture of omega-3 and omega-6 fatty acids can inhibit the anorexia induced by CCK-8 (Yehuda and Mostofsky, 2004), while a high-fat diet increases the potency of CCK-8 (Torregrossa and Smith, 2003).

Leptin is a 146-amino-acid protein; it is a product of the obese (OB) gene, and is secreted by adipocytes in proportion to fat mass. Leptin decreases food intake and increases energy expenditure by affecting the balance between orexigenic (appetite reducting) and anorexigenic (appetite enhancing) hypothalamic pathways (Mistry, et al., 1997, Banks, 2011, Engineer and Garcia, 2011). Leptin resistance is one mechanism that induces obesity. Fatty acids enhance leptin release and activity (Di Benedito, et al., 2009, McCullough, et al., 2011).

Fewer studies have examined the role of the 30-amino-acid peptide glucagon-like peptide 1 (GLP-1) (Dossant, et al., 2011) and the 41-amino-acid peptide corticotropin-releasing factor (CRF) (Hassen and Hassen, 2011). Omega-3 fatty acids enhance the release and activity of orexigenic neuropeptides, and inhibit anorexigenic neuropeptides and proinflammatory cytokines (Goncalves, et al., 2005).

Cytokines and anorexia

There is a strong connection between severe reduction in food intake and major changes in cytokine activity. Increases in the levels of proinflammatory cytokines [interleukin (IL)-1, IL-4, Il-6, IL-10, and tumor necrosis factor alpha (TNF-α)] (Crocos, et al., 2001) were observed in anorexic patients, with parallel reduction in the anti-inflammatory cytokine IL-2. These findings, recently confirmed with the addition that the level of proinflammatory cytokine IL-17 also increased (Ahmed and Geffen, 2010, Stevanovic, et al., 2012), might indicate that anorexia is a state of stress and inflammation.

Complaints about sleep disorders are frequent among anorexia patients (Cinosi, et al., 2011, Tzischinskyy and Latzer, 2009). It is interest to note that similar disturbed cytokines profiles (e.g., increases in proinflammatory cytokines and decreased in anti-inflammatory cytokines) have been observed in studies of experimentally induced REM sleep deprivation. Significant increases in IL-1, IL-6, IL-17, and TNF-α were observed, accompanied by a decrease in IL-2. Pretreatment with a mixture of omega-3 and omega-6 fatty acids rehabilitated the behavioral and immunological effects of sleep deprivation (Yehuda, et al., 2007, 2009).

Fatty acid profile and membrane fluidity

A study by Holman et al. (1995) was one of the first to indicate that the fatty acid profile of anorexia patients differs from that of non-anorexic individuals. The study reported a marked decrease in omega-3 and omega-6 fatty acids and an increase in other types of fatty acids. This finding was confirmed by Zak et al. (2005), who observed a marked decrease in LA and ALA and an increase in palmitic acid. Similar results were reported by Potois et al. (2009).

Ethyl eicosapentaenoic acid (E-EPA, an omega-3 fatty acid) has been suggested as a treatment for anorexia nervosa (Ayton, et al., 2004). Swenne and Rosling (2012) recently reported that rehabilitated anorexic girls exhibited normal fatty acid profiles.

Modifications in PUFA composition can alter the membrane fluidity index and affect neuronal membrane functions (Carrie et al., 2009). Changes in fatty acid profile are not limited to the peripheral blood; they also occur in the brain. Holman et al. (1995) noted a reduction in the neuronal membrane fluidity index. Those findings were confirmed later (Caspar-Bauguil, et al., 2012, Walczewska, et al., 2011, Wockel, et al., 2007).

Using erythrocyte membrane as a model for the neuronal membrane, some researchers have demonstrated differences in the erythrocyte membrane fluid index of anorexia patients, which return to normal after re-feeding (Lejoyeux, et al., 1996, Swenne, et al., 2001). Recently, an MRI study confirmed the observed modification of the neuronal membrane index in anorexia patients (Blasel, et al., 2012).

Cognition, anorexia, and fatty acids

Cognitive deficits in anorexia patients have been widely recognized. Although there might be several reasons for cognitive decline in the context of anorexia, three specific reasons appear to partially explain this finding. The first is fatigue due to under-nutrition.(Melchiorri and, Rainoldi, 2008). A Second, deficiencies in EFAs have been shown to induce cognitive deficiency. Conversely, PUFA supplementation can improve learning and memory deficits (Yehuda, et al., 1999, Yehuda, 2012), and omega-3 fatty acid supplementation can improve cognitive decline (Avraham, et al., 2011, Huang, et al., 2011. Third, homocysteine levels are very high among anorexic individuals (Friedlin, et al., 2005). High levels of homocysteine have

been correlated with cognitive decline and Alzheimer's disease (de Lue, et al., 2010). Fatty acid treatment can reduce elevated homocysteine levels in anorexia patients (Wilhelm, et al., 2010).

OBESITY

High-fat diet and stress

Some types of stress can induce obesity (Figer, et al., 2012; Schultz, et al., 2012). A high-fat diet is responsible for insulin resistance, increased insulin levels, and the production of several glucocorticoids, primarily cortisol (Greenwood and Winocur, 2005). Although the effects of a high-fat diet on the cardiovascular system are serious and take various forms, such a discussion is beyond the scope of this review. To the list of deleterious consequences of such a diet, we must add the complications brought on by internal and external stressors, which interact with and aggravate the effects of a high-fat diet. While organisms fed a high-fat diet are already exposed to stress by the diet itself, they respond poorly to any additional stress. When subjected to a stressful test, they exhibit elevated levels of cortisol, ACTH, glucose, and fatty acids (Tennenbaum, et al., 1997). Continued feeding of a high-fat diet to rats results in impaired ability to restore basal corticosterone after the removal of stress (Kamara, et al., 2003). In the long term a high-fat diet can result in both obesity and diabetes. Both humans and animals that are obese and diabetic show an increased level of cortisol and a reduced capacity to handle stress (Gluck, et al., Mota, et al., 2004, Wan, 2005).

The effects of PUFAs on high-fat diet

We have observed that feeding rats a high-fat diet (56% of energy from fat, 4.78 kcal/k) for 4 weeks led to excessive weight gain, as well as poor performance in the Morris Water Maze, passive avoidance, and poor motor activity in open field tests, with hypothermia and phase shifts

in body temperature and circadian cycle (unpublished results). Rats fed a high-fat diet exhibited increased cholesterol and reduced n-3 fatty acids in both the peripheral blood and the neuronal membrane. In addition, corticosterone and IL-1 levels were increased, and IL-2 and IL-10 levels were decreased. To overcome the weight gain, we treated another group of high-fat-diet rats with a daily injection of a mixture of EFAs [a 1:4 ratio of ALA (18:3n-3), and LA (18:3 n-6)]. This treatment rehabilitated most effects of the high-fat diet, as the rats did not gain as much weight as those on the high-fat diet alone, and their performances in the Morris Water Maze, passive avoidance learning, and the open field test were similar to those of control rats. Treated rats also exhibited a normal body temperature and normal circadian cycle, with lower levels of cholesterol and IL-1, and significant increases in IL-2 and IL-10. Clearly, fatty acids have multiple modes of action on cognitive functions, including effects on the HPA axis, the production of cholesterol and cortisol (via p450 enzymes), and improving the ratio of anti-inflammatory agents IL-10 and IL-1. The pro-inflammatory cytokine IL-1 inhibits the role of the brain neurotransmitters, including dopamine, which is responsible for many homeostatic functions and for reinforcement systems that are important for learning (stress produces cortisol, which is toxic to brain areas that are involved in learning and memory). The beneficial effects of n-3 fatty acids on body weight have been reported elsewhere (Nettleton and Katz, 2005) and confirmed (Buckley, et al., 2010, Goulb, et al., 2011, Cintra, et al., 2012).

High-fat diet, diabetes, and learning

Morley and Banks (2010) confirmed earlier studies (Wincour and Greenwood 1999) indicating that high-fat diets induce deficits in learning and memory in the T-maze, foot shock

avoidance, and operant lever press performance tests. In addition, diabetic rats exhibited deficits in other types of learning, such as "conditioned place preference" (Figlewicz, et al., 2004).

The prevalence of diabetes is higher among anorectics than the prevalence in the general population (Birk and Spencer, 1989). The increasing number of aged diabetic patients makes this information particularly interesting; Alzheimer's disease and diabetes appear to be the main age-related disorders. Aged diabetics have exhibited accelerated failed memory, as well as deficits in spatial learning associated with oxidative stress (Anstey and Low, 2004, Biessels, et al., 2002, Hassing, et al., 2004, Kesavadev, et al., 2003, Sandeep, et al., 2005). Several modes of action (e.g., general mechanisms of oxidative stress, cardiovascular changes, non-enzymatic protein glycation, calcium homeostasis, and insulin level) have been proposed to explain the observed effects on learning and cognition (Biessels, et al., 2002). Two possible modes of action deserve special attention: the effect on the hippocampus and the suggestion that GLP-1 mediates learning and memory.

Hippocampus

The hippocampus is involved in episodic, declarative, contextual, and spatial learning and memory. The hippocampus has exhibited atrophy in diabetic animal models (McEwen, et al., 2002), and chronic stress leads to the loss of hippocampal neurons and dendrites (McEwen and Sapolsky, 1995). The atrophy of hippocampal dendrites causes damage to pyramidal neurons and interferes with synaptic activity. The results of this morphological and functional hippocampal damage very likely account for the learning deficits (Yehuda, 2003). The combination of high-fat diet and chronic stress causes hippocampal dendrites to retract (Baran, et al., 2005). The diabetic brain undergoes major structural changes accompanied by abnormal electrophysiological activity

(Biesseles, et al., 2002). However, given that the hippocampus is highly vulnerable to high levels of cortisol and other glucocorticoids, the changes in the hippocampus are likely responsible for the learning deficits.

15.3.2. GLP-1

GLP-1 is a 37-amino-acid peptide and a known regulator of energy metabolism. GLP-1 is centrally involved in the regulation of hippocampal neuronal plasticity and cell survival (Gilman, et al., 2003) and appears to be to be involved in diabetes and obesity. It was suggested recently that GLP-1 might have an important role in memory and learning (During, et al., 2003, Mattson, et al., 2003). Stimulation of GLP-1 can improve learning and memory, and mice deficient in GLP-1 exhibit spatial and associative learning deficits. Interestingly, diabetic individuals experienced a deficiency in GLP-1 production and secretion that might also explain the learning deficits (Vaag, 1994). High- and low-fat diets modified the level of GLP-1 in the serum (Numao, et al., 2012).

The immune system

Repeated demonstrations that PUFAs can modify the production and activity of various components of the immune system have left unexplained the mode of action by which PUFAs exerts their effects. The mediation of immunological functions and cytokine levels by PUFAs is evident in several disorders, such as Alzheimer's disease and schizophrenia (Yano and Van Kammen, 2004). Several mechanisms have been proposed, including changes in membrane fluidity (which might effect the capability of cytokines to bind to their respective receptors on the cell membrane); lipid peroxidation (decreases in free-radical-induced tissue damage); prostaglandin production (an indirect mechanism whereby prostaglandins, which are derivatives

of PUFAs, modify cytokine activity); and the regulation of gene expression (PUFAs influence signal transudation pathways and modified mRNA activity). The role of PUFAs in immune function is complicated by the fact that n-3 and n-6 PUFAs have differential effects on various immune components. A recent review indicated that n-3 fatty acids induce decreases in lymphocyte proliferation in humans and rats, IL-1 production, and IL-2 production in both humans and animals (Singer, 1991). In addition, n-3 fatty acids decrease TNFα production in humans but increase it in mice macrophages, and also decrease natural killer (NK) cell activity. In comparison, n-6 fatty acids increase IL-2 production, decrease TNFα production, and decrease NK cell activity in mice. Still, other studies have shown that LA (an n-6 fatty acid) decreases IL-2 activity (Yehuda, at al, 1997) and increases IL-1 production and tissue response to cytokines, while n-3 fatty acids generally decrease IL-1 production and activity (Grimble, 1998). Although there is some disagreement among studies, it appears that n-3 fatty acids (ALA, DHA, and EPA) decrease the production and activity of the proinflammatory cytokines IL-1, IL-6, and TNFα (Blok, et al.,1997, Chavali, et al., 1998, Hughs and Pinder, 1997, Yano, et al., 2000), while the n-6 family has the opposite effect (Caughey, et al., 1996, Grimble, 1998). The ability of n-3 PUFAs to reduce proinflammatory cytokines and prostaglandins (Chavali and Forse, 1999) leads to a proposal that fish oil be used to relieve pain. Fish oil, rich in n-3 PUFAs, has been shown to decrease IL-6, IL-10, IL-12, TNFα, and prostaglandin E2 (Desinova, et al., 2001).

Increasingly, the salutary effects of PUFAs are being examined not only with respect to their absolute level in diet, supplementation, and serum and tissue content, but also with respect to their proportional relationship to other fatty acids. One example of the critical nature and

importance of a proper ratio can be seen in the increase of anti-inflammatory IL-2 production after treatment with a mixture of n-3 and n-6 fatty acids prepared in a ratio of 1:4 (Yehuda, et al., 1999), together with an increase in n-3 in the tissue (James, et al., 2000).

A high-fat diet increases the level and activity of IL-1 and IL-1 receptors. Moreover, IL-1 administration promotes the effects of high-fat diets (Chi, et al., 2004). Obesity increases the level and activity of IL-6 (Das, 2004, Klove, et al., 2005). A high-fat diet also induces a decrease in IL-2 production (Han, et al., 2002, Mito, et al., 2000, Pompos and Fritsche, 2002). Studies show that a high-fat diet increases the level and activity of proinflammatory cytokines and decreases the level of anti-inflammatory cytokines. Similar effects on the immune system have been reported in diabetes and stress. Proinflammatory cytokines impair learning (Brennan, et al., 1996) and can also affect mood and promote depression (Anisman, et al., 2005).
Under certain conditions, the proinflammatory cytokine IL-17 may induce obesity. Under other conditions, IL-17 is also involved in anorexia. The proinflammatory cytokines appear to be involved in both anorexia and obesity (Ahemed and Geffen, 2010).

The BBB and obesity

The BBB controls the permeability of substances and molecules from the peripheral blood into the brain. Therefore, the BBB is a key factor in the bioavailability of essential molecules to the brain, especially those molecules that the brain cannot synthesize. While only a few studies have been completed on the topic, stress, obesity, and diabetes each appear to induce an increase in the permeability of the BBB (Banks, 2004, 2008, 2010, Esposito, et al., 2001). Additional studies are needed to evaluate the effects that changes in the BBB may have on those states.

Conclusion

The surprising outcome of this review is that anorexia and binge eating disorder are in some sense two diseases on a continuum: anorexia is a condition characterized by underfeeding, while binge eating disorder is characterized by overfeeding. However, these two disorders share many variables, which are summarized in Table 1. It is clear that anorexia and binge eating disorder share many physiological, biochemical, immunological, and behavioral variables, to which the common denominators are stress and inflammation-like states.

The ability of omega-3/omega-6 fatty acid supplementation to interfere in two apparently opposite disorders can be explained by the pivotal role of EFAs in stabilizing the neuronal membrane fluidly index. This review might contribute to a better understanding the biological bases of both anorexia and binge eating disorder, and may lead to better treatment of both conditions.

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Table 1 The differences and similarities between Anorexia and Obesity

	Anorexia	Obesity
Food intake	Decreased	Increased
Blood Brain Barrier	**Disturbed**	**Disturbed**
Dopamine, Serotonin	**Involved**	**Involved**
Peptides	Decrease appetite orexigenic neuropeptides	Increase appetite anorexigenic neuropeptides
Stress	**Induced**	**Induced**
Stress hormones CRF, Cortisol	**Increased**	**Increased**
Cytokines	**Increases inflammatory cytokines**	**Increases inflammatory cytokines**
Cognition	**Deficits**	**Deficits**
Sleep disturbances	**Yes**	**Yes**
Essential fatty acid involvement	**Yes**	**Yes**
Fatty acid supplements as treatment	**Yes**	**Yes**