Published in final edited form as:

Med Hypotheses. 2011 December ; 77(6): 1114–1120. doi:10.1016/j.mehy.2011.09.016.

Greasing the Wheels of Managing Overweight and Obesity with Omega-3 Fatty Acids

N Golub¹, D Geba¹, SA Mousa², G Williams³, and RC Block⁴

¹The University of Rochester School of Medicine and Dentistry, Rochester, New York

²Pharmaceutical Research Institute, Albany College of Pharmacy and Health Sciences, Albany, New York

³Center for Community Health, Department of Medicine, the University of Rochester School of Medicine and Dentistry, Rochester, New York

⁴Department of Community and Preventive Medicine and the Cardiology Division, Department of Medicine, the University of Rochester School of Medicine and Dentistry, Rochester, New York

Abstract

The epidemic of overweight and obesity around the world and in the US is a major public health challenge, with 1.5 billion overweight and obese adults worldwide, and 68% of US adults and 31% of US children and adolescents overweight or obese. Obesity leads to serious health consequences, including an increased risk of type 2 diabetes mellitus and heart disease. Current preventive and medical treatments include lifestyle modification, medication, and bariatric surgery in extreme cases; however, they are either not very efficacious or are very expensive. Obesity is a complex condition involving the dysregulation of several organ systems and molecular pathways, including adipose tissue, the pancreas, the gastrointestinal tract, and the CNS. The role of the CNS in obesity is receiving more attention as obesity rates rise and treatments continue to fail. While the role of the hypothalamus in regulation of appetite and food intake has long been recognized, the roles of the CNS reward systems are beginning to be examined as the role of environmental influences on energy balance are explored.

Omega-3 polyunsaturated fatty acids are essential nutrients that play a beneficial role in several disease processes due to their anti-inflammatory effects, modulation of lipids, and effects on the CNS. Omega-3 fatty acids, specifically EPA and DHA, have shown promising preliminary results in animal and human studies in the prevention and treatment of obesity. Given their effects on many of the pathways involved in obesity, and specifically in the endocannabinoid and mesocorticolimbic pathways, we hypothesize that EPA and DHA supplementation in populations can reduce the reward associated with food, thereby reduce appetite and food intake, and ultimately contribute to the prevention or reduction of obesity. If these fatty acids do harbor such

© 2011 Elsevier Ltd. All rights reserved.

Corresponding Author: Robert C. Block, MD, MPH, Department of Community and Preventive Medicine, Box 644, 601 Elmwood Avenue, Rochester, New York 14642, (585) 275-3356 (phone), robert_block@urmc.rochester.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

CONFLICTS OF INTEREST

The authors declare that there are no potential conflicts of interest including employment, salary, consulting fees, honoraria, stock or equity interests, expert testimony, and intellectual property rights (e.g., patents, royalties, copyrights). None of the authors have professional or financial affiliations that may potentially be regarded as having biased the manuscript.

potential, their supplementation in many parts of the world may hold great promise in reducing the global burden of obesity.

The Problems of Overweight and Obesity

Known from ancient times and considered traditionally a disease of affluent individuals, obesity is currently highly prevalent in both developed and developing regions of the globe [1, 2]. The number of overweight and obese individuals has increased at an alarming rate worldwide in the last few decades, being declared at epidemic levels since 1997[3]. In 2008, approximately 1 billion adults in the world were overweight, and 500 million were obese [4]. The World Health Organization (WHO) defines obesity as a condition of excess body fat to the extent that health is impaired[3, 5]. In the US, obesity prevalence is at an all-time high, with approximately one third of adults considered obese[6].

Obesity is commonly measured using body mass index (BMI, weight/height²). In pediatric populations, BMI values ranging from the 85th to the 95th percentile for age and sex define overweight, while values at or above the 95th percentile define obesity [7]. In adults, the definition of obesity is based on absolute values of BMI, overweight being a BMI between >25 and 29.9 kg/m², and obese being a BMI >30 kg/m² [8]. National Health and Nutrition Examination Survey (NHANES) data show that between 1970 and 2000, the prevalence of overweight in children aged 2 to 19 years in the US increased from 10% to 15%, and the prevalence of obesity in this population tripled, from 5% to 15%[9]. In adults ages 20–74, the prevalence of overweight increased from 31.5% in 1960–1962 to 32.3% in 2005–2006, and the prevalence of obesity increased from 13.4% to 35.1% in the same time periods[6]. Among adults, a greater proportion of men (41.2%) are overweight compared to women (28.4%), and women are more likely than men to be obese or extremely obese [10]. Prevalence of overweight and obesity is disproportionately higher among individuals of lower socioeconomic status and among minority groups like African-Americans, Hispanics, and Native-Americans [10, 11]. While no gender differences in obesity prevalence have been observed in the pediatric population, the discrepancies according to race/ethnicity and socioeconomic status mirror those of the adult population.

The causes of obesity are multifactorial. Most cases of obesity are caused by the imbalance between energy intake and expenditure [12, 13], and a small proportion of obesity cases are secondary to medical conditions (e.g., Prader-Willi syndrome or Cushing syndrome), or are treatment-related (e.g., treatment with antidepressants or anticonvulsants). Changes brought by industrialization, with their negative influences on both diet and physical activity levels, explain, at least in part, the increasing trends in obesity prevalence seen during the last decades. Like other chronic diseases, the worldwide spread of the obesity epidemic is the consequence of the fact that it has followed the model of the epidemiologic transition [14, 15].

Complications of Obesity

Complications of obesity in adults include dyslipidemia, type 2 diabetes mellitus, coronary heart disease, hypertension, cancer, and premature death [16–19]. Along with the increasing prevalence of obesity in recent decades, complications of obesity rarely seen in the pediatric population, such as type 2 diabetes, hypertension, dyslipidemia, cardiovascular disease, and metabolic syndrome are becoming more common [20, 21]. Consequently, more high quality and productive life years are lost with the shift of these diseases to earlier in the life span [22, 23]. Additionally, the excess weight gained early in life is usually difficult to lose, as overweight and obesity in childhood tracks into adulthood [24–26]. Based on these

considerations, in 2004, the Institute of Medicine introduced its laudable initiative to consider the prevention of obesity in children a national priority [27].

The multitude of complications from obesity not only causes human suffering, but also determines the staggering economical costs associated with obesity. Depending on the mathematical model used to estimate the costs, they range between about 6% [28] and 16% [29] of total health care expenditures in the US. Given the relentlessly increasing prevalence of obesity, these costs are likely to increase. Therefore, it is imperative to increase efforts to address the current obesity epidemic. These efforts should be directed toward developing and implementing interventions aimed at reducing the prevalence of overweight and obesity in adults and preventing their development in the pediatric population.

Challenges Inherent in Reducing Overweight and Obesity

Aligned with these strategies, numerous interventions have been carried out in the pediatric and adult populations, with most reporting only marginal success. A recent Cochrane review examined evidence from 22 randomized controlled trials lasting from 12 weeks to 3 years that aimed to reduce overweight and obesity in children under 18 years old [30]. The trials were predominantly school-based and included children ranging from 7 to 12 years old; some examined the roles of increasing physical activity levels or improving diet, and some examined their combined effect on BMI. Although most trials found an improvement in the amount of physical activity or healthy eating habits, only a few found an impact on BMI. The authors concluded that there was not enough evidence that any of the interventions were successful in preventing or reducing overweight/obesity, and point to methodological issues in the studies, their short duration, and the complexity of preventing obesity as reasons for lack of efficacy. Another review of interventions in children ages 0 to 5 found similar results [31, 32]. Some researchers have emphasized the importance of a family component to improving the effectiveness of interventions to reduce overweight and obesity [32–34], as well as the greater success of interventions with multiple components that address the multifactorial causes of obesity [34]. A number of studies have examined the prevention or reduction of overweight and obesity in adults, and, as in children, showed inconclusive evidence of efficacy [35, 36].

Not only is weight loss hard to achieve, but it is even more difficult to maintain, with most dieters back to baseline weight within 3 to 5 years from intervention [37, 38]. This suggests that weight loss interventions need to be not only more sustainable for patient and medical providers but also better tolerated and physiologically effective. While changes at the level of individual behavior are necessary in order to prevent overweight and obesity, changes at the policy and societal level are also critical in order to address the availability of affordable and quality foods, safe and accessible places to engage in physical activity, and other upstream factors [39].

Concerns raised due to the increasing obesity prevalence are reflected in the growing body of publications in recent years pertaining to this topic, some articulating theories regarding the multifactorial cause of the disease. While changes over time in levels of physical activity among different segments of the US population have played an important role, most sources suggest the paramount importance of changes related to diet, including availability and food costs, food preparation techniques, food composition and diversity, and a progressive replacement of in-home cooked meals with ready-to-eat snacks, and restaurant and fast-food meals [40]. During a period of 17 years from 1977–1978 to 1994–1996, the average daily energy intake increased about 268 calories for men and 143 calories for women [41]. While this increase may seem moderate, sustained over time and combined with the effect of other dietary changes and the concomitant reduction in physical activity at the population level, it

provides a plausible explanation for the weight gain observed among Americans in recent decades.

This paper will address appetite and food intake, and their role in obesity in the context of great food availability. Appetite and food intake are two closely related concepts, and are defined in the current work as the subjective desire to ingest food, felt as hunger, and the objective physical intake of food, respectively. We hypothesize that the ingestion of fish omega-3 fatty acids has the potential of reducing appetite, food intake, and ultimately reducing overweight and obesity. These fatty acids have other known health benefits and we describe later in this article why we believe their advantages include the regulation of appetite in positive ways.

Appetite and Food Intake Regulation and Obesity

Appetite and food intake are complex processes involving multiple organ systems. When food enters the gastrointestinal tract, information on pH, gastric stretch, and changes in nutrient composition are relayed by the vagus nerve to several areas of the brain, including the medulla, hypothalamus, amygdala, and thalamus [42]. These signals are involved in the regulation of feeding. In addition, the gastrointestinal tract secretes hormones that control feeding by acting on the brain. For example, cholecystokinin secretion is a satiety signal for the brain, and ghrelin secretion acts on the hypothalamus to stimulate feeding.

A key hormone in appetite and metabolism regulation is leptin, which is released from adipose tissue. The amount of leptin in the body is increased by higher fat mass, and decreases with decreased fat mass. Leptin acts on the hypothalamus to inhibit the orexigenic effects of the peptides neuropeptide Y (NPY) and agouti-related peptide (AgRP), and activates the anorexigenic effects of downstream targets of pro-opiomelanocortin (POMC) and cocaine-amphetamine regulated transcript (CART). Together, this leads to satiety, and stimulates energy expenditure and ultimately weight loss. Individuals who are obese have high leptin levels, but have decreased responsiveness to leptin signaling, also known as leptin resistance. Another key hormone in regulation of adiposity is insulin, which is secreted from the pancreas in response to feeding. Similar to leptin, insulin acts on the hypothalamus to inhibit NPY and AGRP, and activates POMC and CART, and obese individuals can develop insulin resistance.

The endocannabinoid pathway is another important player in regulation of appetite and metabolism [42]. Endocannabinoids are lipids derived from the omega-6 polyunsaturated fatty acid, arachidonic acid. Levels of endocannabinoids are regulated by dietary intake of essential fatty acids, and the activity of biosynthetic and catabolic enzymes involved in the endocannabinoid pathway [43]. Endocannabinoids activate endogenous cannabinoid CB1 and CB2 receptors in the brain, liver, adipose tissue, and gastrointestinal tract [44]. Activation of CB1 receptors in the hypothalamus leads to increased appetite and food intake by inhibiting the anorexigenic signals of corticotrophin-releasing hormone (CRH) and CART, and activating the orexigenic signal of melanin-concentrating hormone (MCH), as well as via other mechanisms [45]. Recent findings from mouse studies showed that endocannabinoids selectively enhance sweet taste, and this increasing palatability of foods is hypothesized to stimulate food intake [46].

In addition to their role in the central nervous system (CNS), endocannabinoids exert complex effects on peripheral tissues to control energy homeostasis [45]. For example, they act on adipose tissue to increase fat accumulation and adipogenesis, and on the pancreas to affect insulin levels and glucose regulation. The endocannabinoid system functions in concert with other systems regulating food intake and energy balance, and is regulated by leptin, insulin, ghrelin, cholecystokinin, and other signals. There is growing evidence from

animal and human studies that an overactive endocannabinoid system contributes to weight gain and diet-induced obesity [43, 45], and targeting this system is a strategy for weight loss. Results from randomized controlled trials in overweight/obese humans have shown that CB1 receptor antagonists such as rimonabant lead to significant weight loss after one year of treatment [47]. However, increased risk of anxiety, depression, and suicidality in individuals taking CB1 antagonists [48] prompted withdrawal of rimonabant from the market.

CNS motivation and reward pathways are also critical in the regulation of appetite and food intake [49]. Fulton defines the concept of reward as “(1) objects or actions that prioritize behaviour and promote the continuation of ongoing actions, (2) increase the behaviours that lead to the procurement and/or consumption of the reward (positive reinforcement), and (3) direct future behavioural actions”. Major neurotransmitter pathways involved in reward are the dopaminergic pathways in the CNS [50]. The mesolimbic pathway sends projections from the ventral tegmental area to the nucleus accumbens, and the mesocortical pathways send dopaminergic fibers from the nucleus accumbens to the prefrontal cortex. These pathways are collectively referred to as the mesocorticolimbic dopamine system. The mesocorticolimbic dopamine system is implicated in regulation of feeding, and manipulation of dopamine levels in the nucleus accumbens and other portions of reward circuitry has been shown to affect the reward associated with food [49]. Specifically, new stimuli or stimuli associated with reward cause release of dopamine in the nucleus accumbens, while dopaminergic fibers projecting from the nucleus accumbens to the prefrontal cortex may inhibit this release of dopamine [50]. Other systems involved in energy intake can act on the mesocorticolimbic dopamine system to modulate food intake. Specifically, endocannabinoids act on the nucleus accumbens to increase food intake [45, 51], leptin and insulin can act directly on mesolimbic dopamine neurons, to decrease desire for food and motivation to feed [52], and opioids and other neurotransmitters such as serotonin, GABA and glutamate also modulate food reward in various ways[49]. The nucleus accumbens shell is critical in coordinating the effects of opioids, endocannabinoids, and neurotransmitters on food intake.

Due to evolutionary forces, there is strict homeostatic control of adiposity in environments of food scarcity, leading to hunger, food seeking behavior, and decreased energy expenditure[53]. However, there is less control over adiposity in environments of food surplus. For example, obesity is characterized by insulin and leptin resistance. Thus while insulin and leptin levels increase with increased adiposity, their traditional action on the CNS to decrease appetite and increase energy expenditure becomes inefficient, and the individual continues to consume food despite a positive energy balance. It is now clear that there is no set point at which the body senses and responds to excess adiposity by reducing energy intake. This set point may change based on genetic factors and environmental stimuli such as presence, palatability, and amount of food. In addition to the homeostatic control of food intake based on energy demands, there is the “non-homeostatic” control of food intake due to the smell, visual, taste stimuli, and rewards that food provides. These inputs can override homeostatic satiety signals by acting on CNS reward pathways[52, 53]. It is important to note that regulation of homeostatic and non-homeostatic feeding involves reward pathways, and thus there is a complex interplay between these systems and energy intake and expenditure. The current food environment in the United States is characterized by the presence of inexpensive, energy-dense and palatable foods, which allows for overconsumption and excess weight gain.

Fish-Derived Omega-3 Fatty Acids

Omega-3 fatty acids (n-3 polyunsaturated fatty acids [PUFA]) are a group of fatty acids that are essential components of the human diet because they cannot be synthesized in amounts

sufficient for health [38]. Three important omega-3 fatty acids are alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). ALA is found in leafy vegetables, walnuts, soybeans, flaxseed, and seed and vegetable oils, and is the omega-3 fatty acid ingested in greatest amount in a typical diet globally. Sources of EPA and DHA are fatty fish such as salmon and mackerel, fish oil supplements, or the conversion of ingested alpha-linolenic acid to DHA or EPA, though evidence implies that the conversion rate is low [54]. EPA and DHA have many potential health benefits, with proven benefits in reducing risk of coronary heart disease [55] Kris-Etherton, 2002 #26}, and potential benefits in the prevention and treatment of other cardiovascular disorders[56], some forms of mental illness [57, 58], inflammatory disorders such as rheumatoid arthritis [59], and insulin resistance [60].

Omega-3 fatty acids are important components of cell membranes [61]. They also play a key role in the development and function of the brain and CNS. Omega-3s, and especially DHA, are necessary for normal cognitive development and vision. DHA is highly concentrated in neuronal cell membranes, and as such plays an important role in neurotransmission; its depletion is associated with abnormalities in the dopaminergic and serotonergic systems, which are involved in regulation of mood and motivation. Omega-3s are also precursors of eicosanoids, which are molecules that have anti-inflammatory actions, promote vasodilation of blood vessels, and inhibit platelet aggregation. These effects, as well as omega-3's modulation of body lipid composition, are key in the protective role that they play in cardiovascular disease.

Formal recommendations have been made by the American Heart Association advocating that all adults eat oily fish at least twice each week, and that patients with documented coronary heart disease consume approximately 1 gram of the 2 fish-derived omega-3 fatty acids EPA and DHA, each day [38]. The American Heart Association also has recently published recommendations for the ingestion of EPA and DHA by individuals with hypertriglyceridemia and prediabetes[62].

EPA and DHA Effects on Animal Brain Endocannabinoid Levels

The ability of essential fatty acids to regulate endocannabinoid levels raises the question of whether DHA and EPA can affect brain endocannabinoids. For instance, mice chronically deficient in n-3 PUFA have significantly lower concentrations of DHA in brain phospholipids, and significantly higher brain levels of the endocannabinoid, arachidonoylglycerol (2-AG), compared to mice with sufficient n-3 PUFA in the diet [63]. In addition, n-3 PUFA supplementation of 10% weight/weight DHA-rich fish oil for 4 weeks in mice led to significantly higher brain DHA levels compared to mice on a low n-3 PUFA diet, and led to a significant decrease in brain 2-AG and brain arachidonic acid. In another study, obese rats were fed for 1 month on a diet supplemented with n-3 PUFA in the form of fish oil or krill oil, at a dose equivalent to 1.8 g/day for a 2000 calorie diet in humans[64]. Rats supplemented with krill oil had a significantly higher concentration of brain EPA and DHA compared to controls and the fish oil group, and had significantly lower levels of 2-AG in the brains compared to controls and the fish oil group, though food intake was not affected. D'Asti et al. found that 10-day old mice from dams on a high fat diet supplemented with n-3 PUFA had marginally lower ($p=.06$) 2-AG levels in the hypothalamus, and significantly lower 2-AG in the hippocampus compared to pups from dams on a control diet and those on a high fat, high n-6 PUFA diet [65]. These studies demonstrate the ability of dietary n-3 PUFA supplementation to affect brain DHA, and decrease brain 2-AG levels, even at a fairly low dose that is comparable to a safe intake of n-3 PUFAs in humans. 2-AG has been shown in animal models of obesity to be involved in

overeating [64], and thus these results suggest that dietary n-3 PUFA supplementation may be able to affect food intake by acting to decrease brain 2-AG.

EPA and DHA Effects on Dopaminergic Systems

Investigations in animals have demonstrated that n-3 PUFA deficiency leads to changes in performance in several behavioral tests [50, 66, 67], such as increased response rates to rewards (including food), and longer extinction times (return of response to baseline after removal of reward) [50]. These observed differences could be due to effects on learning, and factors that affect learning such as sensory and motor abilities, motivation, arousal and attention [50]. Some investigators postulate that the increased response to reinforcement and slower extinction may be due to changes in motivation in n-3 deficient animals [50, 66]. There is growing evidence that these changes in n-3 PUFA deficient animals are in part due to alteration of dopaminergic systems in the brain. Chalon et al. carried out a series of experiments investigating the effects of chronic n-3 PUFA deficiency on dopaminergic neurotransmission [66, 68]. Rats on a diet deficient in ALA, the precursor of n-3 PUFAs, had a 70% reduction in n-3 PUFA in brain phospholipids, with a subsequent increase in brain n-6 PUFA. Alterations in dopaminergic neurotransmission included reduction in the vesicular monoamine transporter in the nucleus accumbens and frontal cortex of deficient rats, a decrease in dopamine D2 receptors in the frontal cortex and increase in the nucleus accumbens, a decrease in basal dopamine release in the frontal cortex, and an increase in the nucleus accumbens. In addition, there was decreased release of dopamine in response to most stimulants of dopamine release (tyramine, amphetamine, GBR12909) in deficient rats.

In reversibility studies, n-3 PUFA deficient rats supplemented with n-3 PUFA had significantly higher total brain n-3 PUFA compared to deficient animals, and had similar brain n-3 PUFA as control animals maintained on an n-3 PUFA rich diet; similar results were obtained for n-3 PUFA levels in the nucleus accumbens and the hippocampus[68]. Deficient rats had a significantly lower release of dopamine in response to tyramine compared to supplemented and control animals in the prefrontal cortex and the nucleus accumbens. Supplemented and control animals had similar release of dopamine, except animals supplemented with n-3 PUFA for the shortest duration (~40 days), who had a significantly lower release of dopamine compared to controls, and similar to that of deficient animals. While the n-3 PUFA deficiency induced in these experiments is severe, and thus it is difficult to predict how more physiological changes in n-3 PUFA will affect dopaminergic transmission in animals and humans, this evidence does show the potential for dietary n-3 PUFA to affect dopaminergic neurotransmission.

Chalon et al. concluded that n-3 PUFA deficiency may lead to an overactive mesolimbic dopamine system, and a hypofunctional mesocortical pathway, which could manifest in changes in behavior relating to reward, motivation, and learning[68]. Similarly, Reisbick postulated that the behavioral changes, namely in attention, motivation, and reaction to reward seen in n-3 PUFA deficient rats are consistent with defects in the mesocorticolimbic dopamine pathway[50]. He proposes that the hypofunction of the mesocortical pathway leads to disinhibition of the mesolimbic pathway, resulting in increased dopamine release, and subsequent increased reactivity to stimuli. Increased activity in an open-field test, faster swimming speeds, and increased time in open arms maze in rodents are cited as supporting this hypothesis.

In humans, n-3 PUFA deficiency is associated with disorders involving dysfunction of dopaminergic systems such as attention deficit hyperactivity disorder (ADHD), and schizophrenia [66, 69]. ADHD is characterized by impulsivity, hyperactivity, and attentional deficits[70]. In addition, changes in response to reinforcement have been described in

children with ADHD, demonstrated by a stronger preference for immediate versus delayed reinforcement, even if the immediate reinforcement is smaller than the delayed reinforcement[71]. Reviews of studies in humans have demonstrated the involvement of the prefrontal cortex, striatal reward pathways, and catecholamines (dopamine and noradrenaline) in ADHD [71–73]. In fact, it has been proposed that the pathophysiology of ADHD involves impaired inhibition of limbic structures by the frontal cortex, and that the efficacy of stimulants (that act to increase dopamine levels) in treatment of ADHD may be due to their ability to restore proper cortical inhibition[74]. Trials examining n-3 PUFA supplementation in individuals with ADHD are conflicting, though some studies do show improvement in symptoms[75].

Schizophrenia is a disorder in which symptoms include hallucinations, delusions, disorganized speech, catatonic behavior, negative symptoms such as flat affect and avolition (lack of motivation), and significant social and occupational dysfunction[70]. Dysfunction of dopamine signaling in mesocorticolimbic structures, including the prefrontal cortex, nucleus accumbens, and amygdala is implicated in the pathophysiology of schizophrenia, and treatment involves dopamine D2 receptor antagonists[76]. Studies of omega-3 fatty acid supplementation have shown promising results in alleviating symptoms and reducing likelihood of psychosis in individuals at high risk of developing schizophrenia, while studies of individuals with established schizophrenia have shown conflicting results[69]. While ADHD and schizophrenia are very complex and differing disorders, there are similarities in terms of the CNS pathways involved and behavioral manifestations to those of animal models of n-3 PUFA deficiency, pointing to the key role that omega-3 fatty acids may play in the normal functioning of the mesocorticolimbic system in humans, and the potential for omega-3 supplements to ameliorate dysfunction in this system.

EPA, DHA, and Obesity

Animal and human studies have shown that EPA and DHA supplementation may be protective against obesity, and may reduce weight gain in already obese animals and humans [77]. Specifically, studies demonstrated a reduction in visceral (epididymal and/or retroperitoneal) fat in rats fed high lipid diets that incorporate n-3 PUFAs [78–83], and the effect was dose-dependent [80].

The reduction in visceral fat was associated with a decrease in adipocyte size [80, 81] and number of adipocytes [83]. The reduction in visceral fat was seen in some studies without changes in energy intake [78, 79, 83, 84], while 3 studies reported a significantly decreased food intake[82, 85, 86] in rats on an n-3 PUFA supplemented diet. On the other hand, perinatal n-3 PUFA deficiency in rats has been associated with significantly increased food intake[87]. In addition, a dopamine-DHA conjugate was found to increase dopamine transport across the blood-brain barrier of mice by 7.5-fold, and led to about 50% reduction in food consumption in mice and rats compared to control animals; the effect persisted for the 3 week duration of the dopamine-DHA conjugate administration [88]. These studies suggest that n-3 PUFA can play a role in regulation of food intake in rodents.

A study of obese rats found that n-3 PUFA supplementation led to a significant, reduction in weight gain compared to controls in the lower and higher dose of n3-PUFA (5.9% and 5.1%, respectively, and rats on the higher dose consumed significantly less food compared to controls [86]. Ruzickova et al. demonstrated an attenuation of weight gain in mice on a high fat diet supplemented with n-3 PUFA, and even weight loss in those on the highest concentration of n3-PUFA. Similarly, aged rats on a high n-3 PUFA diet for 4 months had a significantly lower body weight compared to those on a diet high in omega-6 fatty acids [89].

There is promising evidence in animal studies that n-3 PUFA supplementation can modulate fat deposition, food intake, and body weight. However, we should use caution when making inferences to the effects of n-3 PUFA in humans, because of possible differences in pharmacokinetics of EPA and DHA supplementation between animals and humans, and because the doses used in animal studies[77] vary widely and are typically higher than those considered safe in humans. For example, Perez-Matute et al. used a dose of 1g/kg/day EPA in rats, while Takahashi and Ide used 85.2 g/kg/day EPA + DHA in rats [82, 85]. A dosage of 1g/kg/day in rats corresponds to 9.6g/day in a 60 kg person[90]. The average intake of omega-3s in the US is approximately 1.6 grams/day (~.7% of energy intake), with 1.4 g of ALA and .2 g of EPA/DHA [91]. The Food and Drug Administration deems intake of up to 3 g/day of marine omega-3s as “generally recognized as safe” [92].

Fewer studies have examined the association between n-3 PUFA intake and adiposity in humans. An observational study of 124 adults found that obese individuals had significantly lower plasma n-3 PUFA concentration compared to healthy weight participants. In obese subjects, there was a significant inverse correlation of $-.4$ between plasma n-3 PUFA and BMI, and correlations of $-.27$ and $-.41$ for waist and hip circumference, respectively [93]. In addition, there was a significant inverse relationship between quartiles of plasma n-3 and BMI, waist, and hip circumference. Studies in youth report significantly decreased plasma n-3 PUFA concentration in overweight youth compared to healthy youth [94], and in obese youth, plasma n-3 PUFA is significantly inversely related to BMI z-score quartiles [95].

Randomized controlled trials in humans examining the relationship between omega-3 supplementation and body composition have found conflicting results[77]. This may be due to differences in study design, the dosage, timing, and duration of n-3 PUFA administration, use of other supplements in addition to n-3 PUFA, and demographics of the study population. Studies that have provided supporting evidence for a role of n-3 PUFAs in body composition are summarized below.

A study of 2-month n-3 PUFA supplementation in 26 overweight or obese postmenopausal women with diabetes found a reduction in body fat mass and a reduction in adipocyte diameter, though no reduction in body weight or total energy intake was seen [96]. An 8-week study of 278 overweight adults found that those on a restricted calorie diet rich in lean or fatty fish or fish oil had a significant reduction in waist circumference and weight compared to individuals on a calorie restricted diet, but this effect was only seen in men [97]. Participants in this study on the high n-3 PUFA diets reported more fullness immediately after a test meal and more fullness and less hunger 2 hours postprandial than those on a low n-3 PUFA diet [98]. This finding supports a potential role for omega-3 in appetite regulation in humans.

HYPOTHESIS: EPA and DHA act on the human mesocorticolimbic pathway and the human endocannabinoid pathway to decrease the reward associated with food, thereby reducing appetite, food intake, and ultimately reducing overweight and obesity

Different organ systems in the body and various pathways are involved in appetite, food intake, and energy homeostasis, and the dysregulation of these systems leads to obesity. These include brain structures such as the brain stem, hypothalamus, and reward pathways, as well as the gastrointestinal tract, adipose tissue, and the pancreas. Increasing evidence suggests that the omega-3 fatty acids EPA and DHA play a role in these organ systems, and especially in the CNS. Studies in animals and humans have shown promising effects of treatment with EPA/DHA supplemented diets to prevent and reduce obesity. These positive effects have mostly been discussed in the realm of the effect of EPA and DHA on metabolic profiles of subjects, i.e., reductions in visceral fat, greater insulin sensitivity, and

improvements in lipid profiles. While the effects of EPA/DHA on the endocannabinoid system and on dopaminergic reward systems in the brain have been described, to our knowledge, no animal or human studies have examined the role of DHA and EPA in modulating these systems to affect appetite and food intake. As the endocannabinoid and mesocorticolimbic pathways play a role in appetite, energy intake and obesity, we hypothesize that, in addition to beneficial effects on metabolism, EPA and DHA regulate the endocannabinoid and mesocorticolimbic dopamine systems in humans to decrease appetite, increase satiety, reduce food intake, and ultimately contribute to prevention or reduction of overweight and obesity. Supporting evidence for this hypothesis includes:

1. EPA and DHA supplementation decreases brain endocannabinoid levels in rodents.
2. EPA and DHA deficiency is associated with dysfunction of the mesocorticolimbic system in animals, and with behavioral changes including motivation and response to reward.
3. EPA and DHA supplementation has been shown to affect dopaminergic transmission in animals, and has shown some preliminary evidence of efficacy in modulating symptoms in humans with disorders of the mesocorticolimbic system.
4. EPA/DHA supplementation affects the modulation of appetite and food intake in some animal and human studies.
5. EPA/DHA supplementation reduces fat mass, and in some cases, weight gain, in animal and human studies.

Further studies are necessary to elucidate the effects of EPA/DHA supplementation on the reward associated with food intake and appetite, food consumption, weight loss, and, at the same time, the molecular effects on the function of the endocannabinoid system and the mesocorticolimbic system. Studies in humans are especially key, because molecular and behavioral changes in animal models may not correspond to the same effects in humans. In addition, the interplay between diets of differing composition of essential fatty acids and effects of EPA/DHA must be examined because the effects of n-3 PUFAs also depend on the ratio of n-3 to n-6 fatty acids, as they are substrates that compete for some of the same enzymes[99].

Given the continuing rise in the worldwide rates of overweight and obesity, with failure of current prevention and treatment paradigms, exploration of other avenues of prevention and treatment is needed. Increasing omega-3 fatty acid intake via changes in diet or via supplementation with fish oil may be one strategy. Although evidence for a role of omega-3 fatty acids in prevention of overweight and obesity is just beginning to be accumulated, the various other health benefits and lack of negative side effects warrant consideration of the need to encourage dietary changes to increase n-3 PUFA or the use of n-3 PUFA supplements at the population level. Even if the effect of n-3 PUFA on overweight and obesity is found to be small, such changes at the level of the individual can lead to significant shifts in the distribution of weight in the population[100]. In addition, since fish oil is inexpensive, safe[38], and few interactions with pharmaceutical drugs exist[101] this approach is potentially very viable as a public health intervention.

Acknowledgments

The authors would like to thank Kelly Keating, PhD, at the Albany College of Pharmacy and Health Sciences, for her assistance in editing the manuscript.

This publication was made possible by Grant Number UL1 RR024160 from the National Center for Research Resources (NCRR), a component of the National Institutes of Health (NIH), and the NIH Roadmap for Medical Research. Its contents are solely the responsibility of the authors and do not necessarily represent the official view

of NCRR or NIH. Information on NCRR is available at <http://www.ncrr.nih.gov/>. Information on Re-engineering the Clinical Research Enterprise can be obtained from <http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp>.

References

1. de Moraes AC, Fadoni RP, Ricardi LM, et al. Prevalence of abdominal obesity in adolescents: a systematic review. *Obes Rev.* 12:69–77. [PubMed: 20524997]
2. Misra A, Khurana L. Obesity and the metabolic syndrome in developing countries. *J Clin Endocrinol Metab.* 2008; 93:S9–S30. [PubMed: 18987276]
3. World Health Organization (WHO). Obesity: preventing and managing the global epidemic. Report of a WHO consultation; World Health Organ Tech Rep Ser. 2000. p. i-xii.p. 1-253.
4. World Health Organization (WHO). [Accessed May 30, 2011] Obesity and Overweight. 2011. <http://www.who.int/mediacentre/factsheets/fs311/en/>
5. Garrow, JS. Obesity and Related Diseases. London: Churchill Livingstone; 1988.
6. National Center for Health Statistics (NCHS). [Accessed April 20, 2010] Prevalence of overweight, obesity, and extreme obesity among adults: United States, trends 1976–80 through 2005–2006. 2008. http://www.cdc.gov/nchs/data/hestat/overweight/overweight_adult.pdf
7. Centers for Disease Control and Prevention (CDC). [Accessed April 24, 2010] About BMI for Children and Teens. 2009. http://www.cdc.gov/healthyweight/assessing/bmi/childrens_bmi/about_childrens_bmi.html
8. Centers for Disease Control and Prevention (CDC). [Accessed April 20, 2010] About BMI for Adults. 2009. http://www.cdc.gov/healthyweight/assessing/bmi/adult_bmi/index.html
9. Anderson PM, Butcher KE. Childhood obesity: trends and potential causes. *Future Child.* 2006; 16:19–45. [PubMed: 16532657]
10. Wang Y, Beydoun MA. The obesity epidemic in the United States--gender, age, socioeconomic, racial/ethnic, and geographic characteristics: a systematic review and meta-regression analysis. *Epidemiol Rev.* 2007; 29:6–28. [PubMed: 17510091]
11. Kuntz B, Lampert T. Socioeconomic factors and obesity. *Dtsch Arztebl Int.* 107:517–522. [PubMed: 20737057]
12. Quilliot D, Roche G, Mohebbi H, Sirvaux MA, Bohme P, Ziegler O. Nonsurgical management of obesity in adults. *Presse Med.* 39:930–944. [PubMed: 20674258]
13. Robinson TN. Television viewing and childhood obesity. *Pediatr Clin North Am.* 2001; 48:1017–1025. [PubMed: 11494635]
14. Yusuf S, Reddy S, Ounpuu S, Anand S. Global burden of cardiovascular diseases: part I: general considerations, the epidemiologic transition, risk factors, and impact of urbanization. *Circulation.* 2001; 104:2746–2753. [PubMed: 11723030]
15. Omran AR. The epidemiologic transition: a theory of the epidemiology of population change. 1971. *Milbank Q.* 2005; 83:731–757. [PubMed: 16279965]
16. Bianchini F, Kaaks R, Vainio H. Overweight, obesity, and cancer risk. *Lancet Oncol.* 2002; 3:565–574. [PubMed: 12217794]
17. Mokdad AH, Ford ES, Bowman BA, et al. Prevalence of obesity, diabetes, and obesity-related health risk factors, 2001. *JAMA.* 2003; 289:76–79. [PubMed: 12503980]
18. McElroy SL, Kotwal R, Malhotra S, Nelson EB, Keck PE, Nemeroff CB. Are mood disorders and obesity related? A review for the mental health professional. *J Clin Psychiatry.* 2004; 65:634–651. quiz 730. [PubMed: 15163249]
19. Woolf AD, Breedveld F, Kvien TK. Controlling the obesity epidemic is important for maintaining musculoskeletal health. *Ann Rheum Dis.* 2006; 65:1401–1402. [PubMed: 17038450]
20. Freedman DS, Dietz WH, Srinivasan SR, Berenson GS. The relation of overweight to cardiovascular risk factors among children and adolescents: the Bogalusa Heart Study. *Pediatrics.* 1999; 103:1175–1182. [PubMed: 10353925]
21. Marcovecchio M, Mohn A, Chiarelli F. Type 2 diabetes mellitus in children and adolescents. *J Endocrinol Invest.* 2005; 28:853–863. [PubMed: 16370570]

22. James PT, Rigby N, Leach R. The obesity epidemic, metabolic syndrome and future prevention strategies. *Eur J Cardiovasc Prev Rehabil.* 2004; 11:3–8. [PubMed: 15167200]
23. Galal OM, Hulett J. Obesity among schoolchildren in developing countries. *Food Nutr Bull.* 2005; 26:S261–S266. [PubMed: 16075576]
24. Field AE, Cook NR, Gillman MW. Weight status in childhood as a predictor of becoming overweight or hypertensive in early adulthood. *Obes Res.* 2005; 13:163–169. [PubMed: 15761176]
25. Nader PR, O'Brien M, Houts R, et al. Identifying risk for obesity in early childhood. *Pediatrics.* 2006; 118:e594–e601. [PubMed: 16950951]
26. Herman KM, Craig CL, Gauvin L, Katzmarzyk PT. Tracking of obesity and physical activity from childhood to adulthood: the Physical Activity Longitudinal Study. *Int J Pediatr Obes.* 2009; 4:281–288. [PubMed: 19922043]
27. Koplan JP, Liverman CT, Kraak VI. Preventing childhood obesity: health in the balance: executive summary. *J Am Diet Assoc.* 2005; 105:131–138. [PubMed: 15635359]
28. Wolf AM, Colditz GA. Current estimates of the economic cost of obesity in the United States. *Obes Res.* 1998; 6:97–106. [PubMed: 9545015]
29. Cawley J, Meyerhoefer C. The Medical Care Costs of Obesity: An Instrumental Variables Approach. 2010 <http://www.nber.org/papers/w16467>.
30. Summerbell CD, Waters E, Edmunds LD, Kelly S, Brown T, Campbell KJ. Interventions for preventing obesity in children. *Cochrane Database Syst Rev.* 2005;CD001871. [PubMed: 16034868]
31. Campbell KJ, Hesketh KD. Strategies which aim to positively impact on weight, physical activity, diet and sedentary behaviours in children from zero to five years. A systematic review of the literature. *Obes Rev.* 2007; 8:327–338. [PubMed: 17578382]
32. Hesketh KD, Campbell KJ. Interventions to prevent obesity in 0–5 year olds: an updated systematic review of the literature. *Obesity (Silver Spring).* 18 Suppl 1:S27–S35. [PubMed: 20107458]
33. Young KM, Northern JJ, Lister KM, Drummond JA, O'Brien WH. A meta-analysis of family-behavioral weight-loss treatments for children. *Clin Psychol Rev.* 2007; 27:240–249. [PubMed: 17070638]
34. Seo DC, Sa J. A meta-analysis of obesity interventions among U.S. minority children. *J Adolesc Health.* 46:309–323. [PubMed: 20307819]
35. Lombard CB, Deeks AA, Teede HJ. A systematic review of interventions aimed at the prevention of weight gain in adults. *Public Health Nutr.* 2009; 12:2236–2246. [PubMed: 19650959]
36. Lemmens VE, Oenema A, Klepp KI, Henriksen HB, Brug J. A systematic review of the evidence regarding efficacy of obesity prevention interventions among adults. *Obes Rev.* 2008; 9:446–455. [PubMed: 18298429]
37. Wing RR, Tate DF, Gorin AA, Raynor HA, Fava JL. A self-regulation program for maintenance of weight loss. *N Engl J Med.* 2006; 355:1563–1571. [PubMed: 17035649]
38. Kris-Etherton PM, Harris WS, Appel LJ. Fish consumption, fish oil, omega-3 fatty acids, and cardiovascular disease. *Circulation.* 2002; 106:2747–2757. [PubMed: 12438303]
39. Caterson ID, Gill TP. Obesity: epidemiology and possible prevention. *Best Pract Res Clin Endocrinol Metab.* 2002; 16:595–610. [PubMed: 12468409]
40. Nielsen SJ, Siega-Riz AM, Popkin BM. Trends in energy intake in U.S. between 1977 and 1996: similar shifts seen across age groups. *Obes Res.* 2002; 10:370–378. [PubMed: 12006636]
41. Cutler DM, Glaeser EL, Shapiro JL. Why Have Americans Become More Obese? *Journal of Economic Perspectives.* 2003; 17:93–118.
42. Ahima RS, Antwi DA. Brain regulation of appetite and satiety. *Endocrinol Metab Clin North Am.* 2008; 37:811–823. [PubMed: 19026933]
43. Banni S, Di Marzo V. Effect of dietary fat on endocannabinoids and related mediators: consequences on energy homeostasis, inflammation and mood. *Mol Nutr Food Res.* 54:82–92. [PubMed: 20013888]

44. Artmann A, Petersen G, Hellgren LI, et al. Influence of dietary fatty acids on endocannabinoid and N-acylethanolamine levels in rat brain, liver and small intestine. *Biochim Biophys Acta*. 2008; 1781:200–212. [PubMed: 18316044]
45. Matias I, Di Marzo V. Endocannabinoids and the control of energy balance. *Trends Endocrinol Metab*. 2007; 18:27–37. [PubMed: 17141520]
46. Yoshida R, Ohkuri T, Jyotaki M, et al. Endocannabinoids selectively enhance sweet taste. *Proc Natl Acad Sci U S A*. 107:935–939. [PubMed: 20080779]
47. Van Gaal L, Pi-Sunyer X, Despres JP, McCarthy C, Scheen A. Efficacy and safety of rimonabant for improvement of multiple cardiometabolic risk factors in overweight/obese patients: pooled 1-year data from the Rimonabant in Obesity (RIO) program. *Diabetes Care*. 2008; 31 Suppl 2:S229–S240. [PubMed: 18227491]
48. Christensen R, Kristensen PK, Bartels EM, Bliddal H, Astrup A. Efficacy and safety of the weight-loss drug rimonabant: a meta-analysis of randomised trials. *Lancet*. 2007; 370:1706–1713. [PubMed: 18022033]
49. Fulton S. Appetite and reward. *Front Neuroendocrinol*. 31:85–103. [PubMed: 19822167]
50. Reisbick S. M., N. Omega-3 Fatty Acid Deficiency and Behavior: A Critical Review and Directions for Future Research. In: Yehuda, S.; Mostofsky, DI., editors. *Handbook of Essential Fatty Acid Biology: Biochemistry, Physiology, and Behavioral Neurobiology*. Towota, NJ: Humana Press; 1997.
51. Kirkham TC. Endocannabinoids in the regulation of appetite and body weight. *Behav Pharmacol*. 2005; 16:297–313. [PubMed: 16148436]
52. Figlewicz DP, Benoit SC. Insulin, leptin, and food reward: update 2008. *Am J Physiol Regul Integr Comp Physiol*. 2009; 296:R9–R19. [PubMed: 18945945]
53. Zheng H, Lenard NR, Shin AC, Berthoud HR. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. *Int J Obes (Lond)*. 2009; 33 Suppl 2:S8–S13. [PubMed: 19528982]
54. Anderson BM, Ma DW. Are all n-3 polyunsaturated fatty acids created equal? *Lipids Health Dis*. 2009; 8:33. [PubMed: 19664246]
55. Wang C, Harris WS, Chung M, et al. n-3 Fatty acids from fish or fish-oil supplements, but not alpha-linolenic acid, benefit cardiovascular disease outcomes in primary- and secondary-prevention studies: a systematic review. *Am J Clin Nutr*. 2006; 84:5–17. [PubMed: 16825676]
56. Skerrett PJ, Hennekens CH. Consumption of fish and fish oils and decreased risk of stroke. *Prev Cardiol*. 2003; 6:38–41. [PubMed: 12624561]
57. Amminger GP, Schafer MR, Papageorgiou K, et al. Long-chain omega-3 fatty acids for indicated prevention of psychotic disorders: a randomized, placebo-controlled trial. *Arch Gen Psychiatry*. 67:146–154. [PubMed: 20124114]
58. Ross BM, Seguin J, Sieswerda LE. Omega-3 fatty acids as treatments for mental illness: which disorder and which fatty acid? *Lipids Health Dis*. 2007; 6:21. [PubMed: 17877810]
59. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev*. 68:280–289. [PubMed: 20500789]
60. Carpentier YA, Portois L, Malaisse WJ. n-3 fatty acids and the metabolic syndrome. *Am J Clin Nutr*. 2006; 83:1499S–1504S. [PubMed: 16841860]
61. Schuchardt JP, Huss M, Stauss-Grabo M, Hahn A. Significance of long-chain polyunsaturated fatty acids (PUFAs) for the development and behaviour of children. *Eur J Pediatr*. 169:149–164. [PubMed: 19672626]
62. Miller M, Stone NJ, Ballantyne C, et al. Triglycerides and Cardiovascular Disease: A Scientific Statement From the American Heart Association. *Circulation*. 123:2292–2333. [PubMed: 21502576]
63. Watanabe S, Doshi M, Hamazaki T. n-3 Polyunsaturated fatty acid (PUFA) deficiency elevates and n-3 PUFA enrichment reduces brain 2-arachidonoylglycerol level in mice. *Prostaglandins Leukot Essent Fatty Acids*. 2003; 69:51–59. [PubMed: 12878451]
64. Di Marzo V, Griinari M, Carta G, et al. Dietary krill oil increases docosahexaenoic acid and reduces 2-arachidonoylglycerol but not N-acylethanolamine levels in the brain of obese Zucker rats. *International Dairy Journal*. 20:231–235.

65. D'Asti E, Long H, Tremblay-Mercier J, et al. Maternal dietary fat determines metabolic profile and the magnitude of endocannabinoid inhibition of the stress response in neonatal rat offspring. *Endocrinology*. 151:1685–1694. [PubMed: 20160134]
66. Chalon S, Vancassel S, Zimmer L, Guilloteau D, Durand G. Polyunsaturated fatty acids and cerebral function: focus on monoaminergic neurotransmission. *Lipids*. 2001; 36:937–944. [PubMed: 11724466]
67. Fedorova I, Salem N Jr. Omega-3 fatty acids and rodent behavior. *Prostaglandins Leukot Essent Fatty Acids*. 2006; 75:271–289. [PubMed: 16973342]
68. Chalon S. Omega-3 fatty acids and monoamine neurotransmission. *Prostaglandins Leukot Essent Fatty Acids*. 2006; 75:259–269. [PubMed: 16963244]
69. Peet M. Omega-3 polyunsaturated fatty acids in the treatment of schizophrenia. *Isr J Psychiatry Relat Sci*. 2008; 45:19–25. [PubMed: 18587166]
70. American Psychiatric Association (APA). *Diagnostic and Statistical Manual of Mental Disorders DSM-IV-TR*. Fourth Edition. Washington, DC: American Psychiatric Press; 1994.
71. Tripp G, Wickens JR. Neurobiology of ADHD. *Neuropharmacology*. 2009; 57:579–589. [PubMed: 19627998]
72. Del Campo N, Chamberlain SR, Sahakian BJ, Robbins TW. The Roles of Dopamine and Noradrenaline in the Pathophysiology and Treatment of Attention-Deficit/Hyperactivity Disorder. *Biol Psychiatry ePUB*. 2011
73. Prince J. Catecholamine dysfunction in attention-deficit/hyperactivity disorder: an update. *J Clin Psychopharmacol*. 2008; 28:S39–S45. [PubMed: 18480676]
74. Faraone SV, Biederman J. Neurobiology of attention-deficit hyperactivity disorder. *Biol Psychiatry*. 1998; 44:951–958. [PubMed: 9821559]
75. Chalon S. The role of fatty acids in the treatment of ADHD. *Neuropharmacology*. 2009; 57:636–639. [PubMed: 19715711]
76. Laviolette SR. Dopamine modulation of emotional processing in cortical and subcortical neural circuits: evidence for a final common pathway in schizophrenia? *Schizophr Bull*. 2007; 33:971–981. [PubMed: 17519393]
77. Buckley JD, Howe PR. Anti-obesity effects of long-chain omega-3 polyunsaturated fatty acids. *Obes Rev*. 2009; 10:648–659. [PubMed: 19460115]
78. Hainault I, Carolotti M, Hajdouch E, Guichard C, Lavau M. Fish oil in a high lard diet prevents obesity, hyperlipemia, and adipocyte insulin resistance in rats. *Ann N Y Acad Sci*. 1993; 683:98–101. [PubMed: 8352478]
79. Baillie RA, Takada R, Nakamura M, Clarke SD. Coordinate induction of peroxisomal acyl-CoA oxidase and UCP-3 by dietary fish oil: a mechanism for decreased body fat deposition. *Prostaglandins Leukot Essent Fatty Acids*. 1999; 60:351–356. [PubMed: 10471120]
80. Belzung F, Raclot T, Groscolas R. Fish oil n-3 fatty acids selectively limit the hypertrophy of abdominal fat depots in growing rats fed high-fat diets. *Am J Physiol*. 1993; 264:R1111–R1118. [PubMed: 8322963]
81. Parrish CC, Pathy DA, Angel A. Dietary fish oils limit adipose tissue hypertrophy in rats. *Metabolism*. 1990; 39:217–219. [PubMed: 2308514]
82. Perez-Matute P, Perez-Echarri N, Martinez JA, Marti A, Moreno-Aliaga MJ. Eicosapentaenoic acid actions on adiposity and insulin resistance in control and high-fat-fed rats: role of apoptosis, adiponectin and tumour necrosis factor- α . *Br J Nutr*. 2007; 97:389–398. [PubMed: 17298710]
83. Ruzickova J, Rossmeisl M, Prazak T, et al. Omega-3 PUFA of marine origin limit diet-induced obesity in mice by reducing cellularity of adipose tissue. *Lipids*. 2004; 39:1177–1185. [PubMed: 15736913]
84. Huang XF, Xin X, McLennan P, Storlien L. Role of fat amount and type in ameliorating diet-induced obesity: insights at the level of hypothalamic arcuate nucleus leptin receptor, neuropeptide Y and pro-opiomelanocortin mRNA expression. *Diabetes Obes Metab*. 2004; 6:35–44. [PubMed: 14686961]
85. Takahashi Y, Ide T. Dietary n-3 fatty acids affect mRNA level of brown adipose tissue uncoupling protein 1, and white adipose tissue leptin and glucose transporter 4 in the rat. *Br J Nutr*. 2000; 84:175–184. [PubMed: 11029968]

86. Hassanali Z, Ametaj BN, Field CJ, Proctor SD, Vine DF. Dietary supplementation of n-3 PUFA reduces weight gain and improves postprandial lipaemia and the associated inflammatory response in the obese JCR:LA-cp rat. *Diabetes Obes Metab.* 12:139–147. [PubMed: 19917068]
87. Mathai ML, Soueid M, Chen N, et al. Does perinatal omega-3 polyunsaturated fatty acid deficiency increase appetite signaling? *Obes Res.* 2004; 12:1886–1894. [PubMed: 15601986]
88. Shashoua VE, Hesse GW. N-docosahexaenoyl, 3 hydroxytyramine: a dopaminergic compound that penetrates the blood-brain barrier and suppresses appetite. *Life Sci.* 1996; 58:1347–1357. [PubMed: 8614292]
89. Cha SH, Fukushima A, Sakuma K, Kagawa Y. Chronic docosahexaenoic acid intake enhances expression of the gene for uncoupling protein 3 and affects pleiotropic mRNA levels in skeletal muscle of aged C57BL/6NJcl mice. *J Nutr.* 2001; 131:2636–2642. [PubMed: 11584083]
90. Food and Drug Administration (FDA). [Accessed April 1, 2011] Guidance for industry: estimating the maximum safe starting dose in initial clinical trials for therapeutics in adult healthy volunteers. 2005. <http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm078932.pdf>
91. Kris-Etherton PM, Taylor DS, Yu-Poth S, et al. Polyunsaturated fatty acids in the food chain in the United States. *Am J Clin Nutr.* 2000; 71:179S–188S. [PubMed: 10617969]
92. Food and Drug Administration (FDA). Substances affirmed as generally recognized as safe: menhaden oil. 1997; 62:30751–30757.
93. Micallef M, Munro I, Phang M, Garg M. Plasma n-3 Polyunsaturated Fatty Acids are negatively associated with obesity. *Br J Nutr.* 2009; 102:1370–1374. [PubMed: 19454127]
94. Klein-Platat C, Draï J, Oujaa M, Schlienger JL, Simon C. Plasma fatty acid composition is associated with the metabolic syndrome and low-grade inflammation in overweight adolescents. *Am J Clin Nutr.* 2005; 82:1178–1184. [PubMed: 16332649]
95. Scaglioni S, Verduci E, Salvioni M, et al. Plasma long-chain fatty acids and the degree of obesity in Italian children. *Acta Paediatr.* 2006; 95:964–969. [PubMed: 16882570]
96. Kabir M, Skurnik G, Naour N, et al. Treatment for 2 mo with n 3 polyunsaturated fatty acids reduces adiposity and some atherogenic factors but does not improve insulin sensitivity in women with type 2 diabetes: a randomized controlled study. *Am J Clin Nutr.* 2007; 86:1670–1679. [PubMed: 18065585]
97. Thorsdottir I, Tomasson H, Gunnarsdottir I, et al. Randomized trial of weight-loss-diets for young adults varying in fish and fish oil content. *Int J Obes (Lond).* 2007; 31:1560–1566. [PubMed: 17502874]
98. Parra D, Ramel A, Bandarra N, Kiely M, Martinez JA, Thorsdottir I. A diet rich in long chain omega-3 fatty acids modulates satiety in overweight and obese volunteers during weight loss. *Appetite.* 2008; 51:676–680. [PubMed: 18602429]
99. Flachs P, Rossmeisl M, Bryhn M, Kopecky J. Cellular and molecular effects of n-3 polyunsaturated fatty acids on adipose tissue biology and metabolism. *Clin Sci (Lond).* 2009; 116:1–16. [PubMed: 19037880]
100. Hill JO. Can a small-changes approach help address the obesity epidemic? A report of the Joint Task Force of the American Society for Nutrition, Institute of Food Technologists, and International Food Information Council. *Am J Clin Nutr.* 2009; 89:477–484. [PubMed: 19088151]
101. Davidson MH, Stein EA, Bays HE, et al. Efficacy and tolerability of adding prescription omega-3 fatty acids 4 g/d to simvastatin 40 mg/d in hypertriglyceridemic patients: an 8-week, randomized, double-blind, placebo-controlled study. *Clin Ther.* 2007; 29:1354–1367. [PubMed: 17825687]