The Influence of Ingested Dietary Fat and Its Affects on the Gut and Brain

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Abstract

Obesity and overeating affect many functions of the body including increasing amounts of certain hormones and the storage of fat. Digestive processes influence the digestion and absorption of fats in the gut and these functions can be altered when overeating occurs or a person is obese. The type of fat and the length of a fatty acid chain also contribute to a person’s ability to digest and store fat appropriately. Physiological responses to fatty acids, the release of insulin and regulation of glucose levels are different in obese people. There are also specific receptors that, when activated or inhibited, can alter physiological responses as well. Many areas of the brain have been shown to be involved in feeding behaviors and to regulate the amount of food ingested during a meal. The hypothalamus, nucleus of the solitary tract, area postrema, and paraventricular nucleus are a few of the important areas of the brain that can be modified by obesity and overeating. Peptides, neurotransmitters, and lesions are able to reverse or excite the functions of the brain that regulate food ingestion. Research is being conducted to try to understand the importance of how dietary fat influences digestive behavior. This paper reviews each of these aspects of the above influences on that ingestion of fat.
Introduction

The gastrointestinal system consists of the accessory organs which include the salivary glands, liver, gallbladder, pancreas, and the gastrointestinal tract (GI tract). The GI tract consists of the mouth, pharynx, esophagus, stomach, small and large intestine. This complex system controls how ingested food enters the body. The GI tract transfers ingested foods to numerous areas of the body (central nervous system, circulatory system, etc.) Ingested foods are broken down from large particles (macromolecules) like proteins and polysaccharides that cannot cross the intestinal wall of the epithelium into smaller components that can be absorbed into the body.

The GI tract begins in the mouth where the ingested food is chewed and large pieces are broken up into smaller pieces that can be swallowed. Saliva moistens the food and dissolves food molecules to create the sensation of taste before it is swallowed. The stomach, the next area of the GI tract, stores macromolecules, dissolves macromolecules, and partially digests macromolecules. The glands along the stomach wall secrete hydrochloric acid. This process aids in digestion by dissolving the food along with help from a protein-digesting enzyme, pepsin.

Digestion, the process of breaking down food, is accomplished by the action of hydrochloric acid secretion in the stomach, production of bile from the liver, and the release of a variety of digestive enzymes by the exocrine glands. Once digestion occurs, digestive enzymes are released into the lumen of the GI tract through secretion. Absorption has not yet occurred until the molecules produced by digestion move from the lumen into the layer of epithelial cells, and finally into the blood. As all of these processes take place, the smooth muscle contractions of the GI tract wall mix the luminal
contents with various secretions and move the contents not secreted from the large intestine to the anus through a process called motility. The GI tract is made to absorb as much of any particular substance as possible in order to provide the body with nutrients; however, it does not regulate the amount of nutrients absorbed or the amount of nutrient concentrations in the internal environment. Regulation of the absorbed nutrients is primarily the function of the kidneys. Therefore, small amounts of certain metabolic end products are excreted via the anus because the majority of ingested material is either digested or absorbed.

The GI tract has its own local nervous system known as the enteric nervous system. The neurons either synapse with other neurons in the myenteric and submucosal plexus or end near smooth muscles in order to regulate digestion and release neurotransmitters such as nitric oxide and ATP. Neural reflexes occur independently from the CNS, but there are nerve fibers from the autonomic nervous system that form branches with the intestinal tract and synapse with neurons in both plexuses. Although commonly thought, not all neural reflexes are initiated by signals within the tract; hunger, emotional state, the sight and the smell of food have significant effects on the GI tract and are mediated by the CNS through the autonomic nervous system.

Hormonal regulation controls the GI system by primarily secreting endocrine cells throughout the epithelium of the stomach and small intestine. The main hormones that act on the GI system are secretin, cholecystokinin (CCK), gastrin, and glucose-dependent insulinotropic peptide which exist in the CNS and gastrointestinal plexus neurons. Each of these hormones participates in the feedback control system that regulates the GI
luminal tract partially as well as multiple target cells. The actions of these hormones will be discussed later in the appropriate sections.

Areas of the brain are also involved in regulating the GI tract as well as controlling sensations of hunger and satiety when eating and digestion occurs. Two primary regions of the brain that regulate the GI tract are the area postrema (AP) and the adjacent nucleus of the solitary tract (NST). Both the AP and NST control ingestive behavior; the AP is permeable to blood-borne signals of nutritional status and both the AP and NST receive primary sensory terminal ions from the abdominal vagus nerve. On the other hand, the NST has a larger output because it transmits its projections to its areas of gustatory processing. Damage to either of these brain regions will produce over consumption of palatable foods (South and Ritter, 1983). The medial hypothalamus (MH), paraventricular nucleus (PVN), and ventromedial hypothalamic nucleus (VMN) are also involved in ingestive behaviors. Damage or lesions to any one of these areas will produce overeating and obesity because the feeding inhibitory pathway is destroyed (South and Ritter, 1983).

**Section I: Dietary fat absorption/digestion**

The types of fat influence the body’s ability to digest or absorb food; digestive processes also play an important role. Many different digestive processes affect the absorption and distribution of dietary fatty acids, such as being lipids. The chain length of free fatty acids influences the absorption; long chains are more easily absorbed than short chains. Conjugated linoleic acid is a component whose interactions with various dietary oils are being studied in order to determine how digestion is influenced by the conjugated linoleic acid. Dietary fish oil is shown to increase adipose tissue weight when
compared to a decrease in weight with conjugated linoleic acid. Fish oil is not the only fatty acid that interacts with high fat diets; soybean oil and palm oil are also shown to increase more fat pad mass because of their increased fatty acid saturation. With diets high in polyunsaturated fatty acids, iron absorption and utilization decrease in opposition to an increase with diets high in saturated fatty acids.

Types of fat affect physiological processes which determine how the fat is digested or absorbed. The reduction of weight caused by conjugated linoleic acid in a diet is from a reduction of cell size rather than an actual reduction of fat cell number. Soy protein is a dietary protein that caused a significant reduction in the concentrations of fat pad weight, cholesterol, triglycerides, and glucose and insulin levels when compared with conjugated linoleic acid. Dietary proteins are not the only contributor to absorption of dietary fatty acids; polymorphisms in specific genes play a significant role as well. Gastrointestinal controls of decreased food intake are also seen in diabetic rats. Other physiological effects such as decreasing in food intake in response to fat in a meal are caused by diabetes in rats.

A variety of different sources of digestion affect the absorption and distribution of dietary fatty acids such as lipids. A study by M. Ramirez et al. (2001) stated that lipids have physical, chemical, and physiological properties that indicate they are important aspects in human nutrition because lipids are soluble in organic solvents but insoluble in water. This process affects digestion, absorption and transport in the blood and metabolism. Such qualities that affect the lipids ability to influence fat absorption are fatty acid chain length (medium chain vs. long chain) and unsaturation number (M. Ramirez et al., 2001).
Chain length of free fatty acids influences its absorption ability. Unsaturated fatty acids and medium-chain fatty acid are more efficiently absorbed than long-chain fatty acids. Medium-chain fatty acids are also able to be absorbed in the stomach for use as an energy source. Dietary triglyceride structures influence the fatty acid components because dietary fat is mainly composed of triglycerides. The use of dietary triglycerides with long-chain saturated fatty acids in the sn-2 position illustrates the importance of the fatty acid distribution and fat absorption. Ramirez et al. (2001) stated that structured triglycerides are found to provide new possibilities for designing specific lipids. The lipids hold a particular purpose in human nutrition, including use with malabsorption and specifically with specific diseases.

Fat digestion occurs in the stomach first and foremost through catalization by lingual or gastric lipase (enzymes). In humans, gastric lipase is present and facilitates the intestinal phase of digestion- acting as an emulsifying agent. Lingual lipase is mainly present in rodents and originates as oral lipase. Pancreatic esters from gastric lipase and the hydrolase completely hydrolyze cholesterol esters form into free fatty acids and cholesterols. These cholesterol esters have been shown to possibly aid in the digestion of triglycerides that contain long-chain polyunsaturated acids. It is evident that dietary phospholipids also absorb and enhance total fat absorption as well as influence the composition and metabolism of lipoproteins. Specifically, as absorbed lipids are re-esterified to form new triglycerides and phospholipids in the smooth endoplasmic reticulum, the triglycerides are able to be synthesized via 2-monoglycerides (M. Ramirez et al., 2001).
The affects of conjugated linoleic acid on obesity were first studied in the middle 1990’s (M. B., Sisk et al., 2001). Interactions with various dietary oils have been investigated in order to determine how digestion is interrupted. Ide (2005) studied dietary fish oil and conjugated linoleic acid interaction. In this situation, mice have a diet made up of 1.0% conjugated linoleic acid. This diet exhibits a great decrease in adipose tissue weight, and serum concentrations of leptin and adiponectin. Conjugated linoleic acid occurs naturally in dairy products and increases energy expenditure and mRNA levels of lipogenic enzymes in the liver. Because of these increases, a down regulation of the expression of adipocyte genes occurs and an increase in serum insulin concentration leads to larger increases in triglyceride levels. This experiment hypothesized that a conjugated linoleic acid-dependent increase in hepatic lipogenesis was the result of a substantial reduction in fat pad mass instead of a direct influence of conjugated linoleic acid on the sterol regulatory element binding protein-1 pathway. The fact that white adipose tissue plays a crucial role in metabolizing and converting glucose to fatty acid storage, which influences the slowing of glucose metabolism in the body from the large decrease in fat pad mass caused by conjugated linoleic acid (Ide, 2005).

Dietary fish oil increases adipose tissue weight while conjugated linoleic acid decreases the weight by approximately ten percent (Ide, 2005). Conjugated linoleic acid is usually shown to profoundly decrease body fat mass. In this study, it is 10trans, 12cis-conjugated linoleic acid and enhances in lipogenesis that is responsible for the reduction in fat pad mass. However, as the combination of conjugated linoleic acid and fish oil interact to increase mRNA levels (conjugated linoleic acid alone reduces mRNA levels) in the liver, the expression levels in the liver were considerably lower than those in
adipose tissue. This action causes an increase in fat pad mass; whereas, conjugated linoleic acid alone decreases the mass. This situation illustrates that fish oil feeding counteracts the conjugated linoleic acid -dependent decrease in fat mass. An increase in fat pad mass leads to a decrease in the mRNA expression of destaurated fatty acids as well. This increase indicates that fish oil causes an increase in the activity of fatty acid oxidation enzymes. The fish oil feeding counteracts the conjugated linoleic acid decrease in fat pad mass. From this study, it has become clear that adipose tissue produces and releases adipocytokines. Adipocytokines play a crucial role in adipocyte function and the possible development of obesity. Such adipocytokines are known as leptin, adiponectin, and resistin- all of which are usually located in the adipose tissue (Ide, 2005).

The hypothesis is supported from the data that the liver disposes of excess glucose by converting to fatty acids and storing the fatty acids as triglycerides. In adipose tissue, excess glucose causes inhibition of hepatic lipogenesis that aggravates glucose intolerance and hyperinsulinemia. Evidence for this data exists in the alpha liver X receptor that plays a role in regulating the expression of genes that involve cholesterol metabolism. When ligand activation and increased expression of this receptor occurs, there is an up-regulation of hepatic lipogenesis. The liver receptor is involved with mechanisms of fish oil as the mRNA levels of cholesterol significantly increase (Ide, 2005).

Another study that involves the interaction of high fat diets and fish oil, but also includes soybean oil, palm oil, exercise and body-weight regulation, adiposity, and metabolism was performed by M. Pellizzon et al. (2002). It is thought that different fatty acids will have opposing affects on body weight, composition, and metabolism. A high
fat diet will normally result in obesity in animals and humans. Saturated fatty acids produce higher rates of weight gain when compared with other fatty acids. Polyunsaturated fatty acids are negatively correlated to induce an increase in body fat in humans or to cause obesity in mice and/or rats. When exercise is combined with a high fat diet, there are positive effects in regard to decreasing the amount of weight gain and absorption of fat, as well as minimize insulin resistance caused by a high fat diet. It is found that soybean oil-fed and palm oil-fed rats weigh significantly more than the fish oil-fed rats. However, fish oil-fed fats have much more body fat mass than the control group. These results signify that there is still weight gain (M. Pellizzon et al., 2002).

As expected, insulin levels in the fish oil group are much lower than the palm oil or soybean oil levels and exercise significantly reduces body weight in the fish oil and palm oil groups. This is expected because exercise reduces internal fat storage in the body. The fish oil diet reduced weight gain as well as fat accumulation because it contains polyunsaturated fatty acids compared to soybean oil (highly saturated fatty acid) that increased fat mass in subcutaneous regions. The dietary fatty acid composition is notably interrelated to cell membrane fatty acid composition because the degree of unsaturation in muscle membrane fatty acid is a determinate of insulin sensitivity. A greater degree of unsaturation index is measured in the fish oil-fed rats indicating why this group has higher insulin insensitivity. In conclusion, fish oil-fed rats have a better response to exercise than the other two groups because of the fish oils long polyunsaturated chain. (M. Pellizzon, 2002).

Iron absorption and utilization decreases when a diet is higher in polyunsaturated fatty acids than with diets with higher saturated fatty acids. This situation is seen in
humans as well as animals with iron deficiencies. A study by Shotton and Droke (2003) examines the affects of diets varying in (n-3) and (n-6) polyunsaturated fatty acids (safflower and flaxseed oil) with a diet higher in (n-9) monounsaturated fatty acids (olive oil) or saturated fat (beef tallow) on iron utilization. The data illustrates that iron utilization and plasma iron are only affected by dietary iron because with more iron in the diet, there is more hemoglobin. However, the results are not statistically significant. Flaxseed oil and olive oil may have an influence on iron status and utilization, and these changes possibly will be related to modifications in iron absorption or fatty acid composition of cellular membranes (Shotton and Droke, 2003).

Conjugated linoleic acid has also enhanced T cell function and proliferation and increases production of interleukin-2. Interleukin-2 is a hormone-like substance that can improve the body’s response to disease. The reduction in weight of fat pads is not the reduction of the fat cell number, but rather the reduction of the cell size. In a study by Sisk et al. (2001), conjugated linoleic acid increased fat pad weight in rats with an obese genotype but reduced fat pad weight in lean rats. This interaction decreased the average cell size of lean rats and increased the average cell size of obese rats. As a result of greater rates and contribution of lipogenesis to depository lipids, the obese rats had greater amounts of palmitic, palmitoleic, and oleic acids in their fat pads. The conjugated linoleic acid causes the obese rats to increase the proportions of large cells and decrease small cells. This action accounts for the increase in fat pad weight; the lean rats have the opposite effect (increase in smaller cells with a decrease in large cells). Also, the tissue levels of conjugated linoleic acid are lower in the obese rats. This observation is assumed to be another reason for the dilution of fatty acids into the larger pad. However, it is
important to recognize the ways conjugated linoleic acid decreased fat in lean rats. This decrease could be a consequence of a normalized glucose tolerance along with the hyperphagia in obese animals. This process would result in more glucose availability as a substrate for enlarged fat mass (Sisk, 2001).

Soy protein, when tested against conjugated linoleic acid and casein, has a more substantial effect on human lipid metabolism. In relation to casein, soy protein reduces serum cholesterol and stimulates fatty acid oxidation. Soy protein stimulates fatty acid oxidation and is used as a dietary protein to enhance the body fat-reducing potential of conjugated linoleic acid. The activity of reducing body fat of conjugated linoleic acid has a better outcome with the protein source being soy protein than casein. Casein was used in the study increased the weight of adipose tissue when combined with conjugated linoleic acid in a dose-dependent manner. Decreases in body fat and plasma glucose levels were also achieved in higher amounts with soy protein. The stabilization of glucose is an indication of the importance of the dietary protein source. (Akahoshi, 2004).

It is not known whether the pathway of conjugated linoleic acid reduces fat inhibition of carcinogens and reductions of immune response is separate or share a common mechanism. It is thought that the cis-10, trans-12 isomer of conjugated linoleic acid is the most probable reason for the reduction of body fat. The metabolic effects that conjugated linoleic acid exerts are unclear, but several hypotheses have been presented. Obese rats have several metabolic abnormalities in regard to lipid metabolism which would account for the decreased tissue levels of conjugated linoleic acid. The decreased tissue levels of conjugated linoleic acid occur because of dilution of fatty acid into their larger fat pads. However, comparing the amount of conjugated linoleic acid on a per pad
basis in lean vs. obese rats, the amount of conjugated linoleic acid was higher in obese rats (Sisk, 2001).

A gene that is thought to play a significant role in the absorption of dietary fatty acids is a polymorphism at codon 54 of the fatty acid-binding protein-2 gene. The influence of the intestinal fatty acid-binding protein polymorphism to stems from the Thr-encoding allele on the gene. This process is linked with the increased secretion of triglycerides and small intestine lipid absorption without modifying glucose uptake or metabolism. In a study by Levy et al. (2001) the polymorphism in the fatty acid binding protein-2 gene and its relationship with intracellular lipid transport was investigated. The Thr-encoding allele was also studied to determine its influences on lipid esterification, secretion of lipoproteins, and also glucose uptake and metabolism. The intestines are the critical site for the transport of alimentary fat in the form of lipoproteins which are eventually packaged as chylomicrons. The absorption and translocation of lipolytic proteins from the endoplasmic reticulum occurs due to the actions of fatty acid-binding proteins and lipid esterification (Levy et al., 2001).

The Thr encoding allele exhibited greater absorption for long-chain fatty acids as compared to intestinal fatty acid-binding proteins (Levy et al., 2001). The allele is associated with insulin resistance and enhanced fat oxidation rates- a factor that contributes to type II diabetes in certain rats. The aim of the study done by Levy et al. (2001) was to investigate the relationship between polymorphisms of intestinal fatty acid-binding proteins and intracellular lipid transport in the human intestine. The study suggests that chylomicrons are the predominant lipoprotein particles that are influenced by the intestinal fatty acid-binding protein polymorphism. Higher levels of lipid
synthesis were found when the Thr-54 fatty acid binding protein was expressed.

Increased availability of free fatty acids from chylomicron degradation, with a fatty acid-
binding protein polymorphism, affected the intermediary metabolism. This process
means that high plasma concentrations of free fatty acids decrease the rate of insulin-
stimulated uptake of glucose in skeletal muscles and therefore, leading to an overall
increase in insulin resistance (Levy, 2001).

Satiety and decreased food intake in diabetic rats causes the fat content in a meal
(Edens & Freidman, 1988). These effects are not seen in normal rats when fat is added to
their meals. This physiological effect was tested by Edens and Freidman (1988) by
examining the effects of ingested corn oil with a meal, gastrointestinal fill, and plasma
triglycerides, glycerol, and ketone bodies. The corn oil used was a form of vegetable oil
in order to increase the fat content of the meal. Diabetic rats have increased capacity to
oxidize lipid fuels which underlies their sensitivity of satiating effects of fat. Triglyceride
levels were ten times higher in diabetic rats than in normal rats, and the levels triglyceride
levels were increased more after oil ingestion (Edens & Freidman, 1988). Plasma
glycerol and plasma ketone levels were also elevated in diabetic rats after oil ingestion.
This action confirms that gastric emptying accelerates and intestinal mass contents
increase in diabetic rats. The oxidation of fatty acids has the ability to reduce or suppress
eating (Edens & Freidman, 1988).

It is also possible that gastrointestinal controls are involved as diabetic rat’s
exhibit gastrointestinal clearance of nutrients. This may contribute to their hyperphagia
and fat in the digestive tract with delays in gastric emptying; decreasing the amount of
feeding. In this study, oil decreased the feeding in the diabetic rats. Contents in the first
and second halves of the small intestine were greater in diabetic rats preceding the oil even though oil feeding decreased the contents. Plasma triglyceride levels significantly rose in diabetics, indicating the absorption of fat from the gastrointestinal tract. During post-absorptive oxidation of the ingested fat, diabetic rats encountered satiating effects from increasing plasma ketone body levels. These results conclude that the satiating effect of a fat containing meal depends on the capacity to oxidize it; a factor that usually reduces fat intake in diabetic rats (Edens & Freidman, 1988).

Along with the experiment above, Horn et al. (1996) also studied the effect of fat on the gastrointestinal tract and its cause of reducing feeding behavior. The conclusions indicate that the rats do not suppress food intake immediately, but after a delay and then only slightly for the remainder of the feeding period. The time of the onset and degree of satiety depends on the route of fat administration. Here again, satiety from ingested fat is related to the post-absorptive appearance and oxidation of ingested fat. The suppression of feeding suggests that there is an intestinal signal for satiety. However, the amount of suppression depends on the way in which gastrointestinal tract receives that fat. Glucose causes a strong inhibition of food intake when it is given through intraintestinal infusion compared to normal emptying into the stomach. This suggests that satiety from fat is due a preabsorptive signal and the results from intravenously infused rats are not of significant importance (Horn et al., 1996).

From the many different aspects that interact with the digestive system, conjugated linoleic acid is repeatedly seen to be a major contributor to the reductions in fat mass and fat cell size. When oil or saturated fatty acids are added to a meal, large increases in weight occur. With diets high in polyunsaturated fatty acids, iron absorption
and utilization decrease as opposed to increases with diets high in saturated fatty acids. Dietary proteins, such as soy proteins are also a promising component of weight loss. The proteins are studied further because of their influence with significant reductions in fat weight, triglycerides, cholesterol, glucose, and insulin levels. Other physiological effects, for example, diabetes in rats is caused by a decrease in food intake in response to fat in a meal. Gastrointestinal controls of decreased food intake are also seen in diabetic rats.

Section II: Physiological Response

The physiological responses of fatty acids, insulin, and glucose, play important roles in the metabolism of mammals and humans. Leptin regulates food intake and energy balance. However, leptin levels are elevated quickly due to its receptors at the blood-brain barrier low saturation level. This low saturation level of specific leptin receptors in the blood-brain barrier regulate the amount of leptin allowed, causing increased obesity. Leptin also reduced the mRNA levels of specific genes that are normally increased in obese mice. Orlistat, a lipase inhibitor, is said to reverse the effects of CCK, increase caloric intake, and reduce feelings of satiety. High levels of neurotensin is another way of increasing fat in a diet and how it is related to weight gain. Finally, the way that haemostatic functions and dietary fat interact with each other to cause dietary lipids can modify haemostatic functions.

Insulin and glucose both play a role in the metabolism of mammals and humans. Their influence on hunger and satiety are displayed as their levels rise and fall before and after an ingested meal. Both insulin and glucose levels rise during the consumption of a meal and gradually decline during the digestion of the meal (Grossman, 1986). Diets rich
in saturated fatty acids increase insulin resistance while polyunsaturated fatty acids prevent insulin resistance by increasing membrane fluidity and GLUT4 transport. Membrane fluidity is how easily materials are able to pass through or transport other items through the cell membrane. Insulin resistance is the ability of one's body to produce insulin with an inability for their bodies to respond to the action of insulin. Humans portray acute and prolonged effects of fatty acids on glucose-stimulated insulin secretion. Humans also portray the effect of a high-fat diet on insulin sensitivity and secretion can result in the development of type II diabetes (Manco et al., 2004).

By suppressing lipolysis and lipid oxidation in obese humans, insulin resistance contributes to the inability to remove lipids. In rats that are fed a high fat diet, the insulin-stimulated glucose uptake ability is impaired in both fat and muscle. Many studies have been conducted to improve the knowledge of this subject. It was found that a daily intake of a diet with fat high in saturated fatty acids may lead to insulin resistance and eventually to type II diabetes in subjects with a genetic predisposition (Manco et al., 2004).

Leptin increases appetite and food intake. If leptin concentrations decrease, weight loss is likely to occur. Adipocytes secrete leptin into the bloodstream in order for leptin to gain access to the hypothalamus and regulate energy balance and food intake. Obese humans have greatly elevated plasma leptin concentrations compared to lean humans. The elevated concentrations of leptin cause saturation of its receptors at the brain barrier and decreased transport of leptin into the brain in obese rats (Burguera, 2000). Besides the hypothalamus, leptin also affects functions of peripheral organs involved in maintaining body composition and mediators of appetite control. In rats,
defects in the leptin signaling system results in obesity. This defect exists as a non-sense mutation in the *ob* gene, and therefore preventing the production of leptin protein (Emond et al., 1999).

The study conducted by Renz et al. (2000) investigated genes responsible for regulating body composition, physiological processes, and the peripheral effects of leptin. Genes that are relevant to obesity are found in the liver, pituitary, hypothalamus, muscle, and fat. The expression levels of genes in these areas can be modified by obesity. The five genes investigated were POMC, PC2, prolactin, HSGP25L2G, and one novel. Obesity increased the expression of mRNA levels in genes PC2 and POMC. However, leptin treatment reduced these levels. Prolactins mRNA levels suppressed obesity three to five fold below the baseline, but leptin increased these levels two to three fold above the baseline. The fourth gene, HSGP25L2G, had a six fold increase of expression above the baseline in obese mice and was suppressed by 50% when leptin was introduced. These results illustrate that leptin alters the hypothalamic gene expression. Leptin is influenced by proteins that are synthesized by the hypothalamus. Leptin is then delivered to the pituitary through hypothalamic-pituitary portal circulation. The mice treated with leptin exhibited no alteration in prolactin mRNA levels. However, the five genes given are all altered in some way by obesity and partially normalized by leptin (Renz et al., 2000).

Lipase is an enzyme that creates free fatty acids, but when lipase is inhibited by Orlistat, less fat absorption was hypothesized to occur. Cholecystokinn (CCK) releases and appetites were studied to confirm whether Orlistat caused a decrease when a high-fat meal was presented. CCK is a gastrointestinal peptide that suppresses food intake or
appetite control. CCK mimics the postprandial state, a reduction of caloric intake, causing a decreased food intake and increased fullness. Its receptor antagonist, CCK-A (Orlistat), stimulates caloric intake and delays the feelings of satiety. When administered, Orlistat should stimulate caloric intake and hunger while delaying the feelings of fullness. An experiment investigated the effect of oral administration of Orlistat on plasma CCK release and measured of behavioral satiety and hunger when presented a high-fat meal. The results indicate that Orlistat does not significantly alter hunger, satiety, or prospective consumption. Alternate conclusions have been given on the significance of CCK and its interaction with obesity. First, the protein content of the meal can act as a factor for CCK secretion and second, variability of CCK is increased in the trials, which is explained by the amount of body fat present and not weight. This provides support for previous research which demonstrates that overweight and/or obese subjects exhibit instances of insensitivity to the satiating effects of fat with a low response to CCK (Goedecke et al., 2003).

Decreased leptin transport across the blood-brain barrier indicates another way in which obesity can occur. The permeability of leptin and the blood-brain barrier in homozygous lean rats, high fat diet-induced obese rats, and genetically obese rats was investigated. The data displays the permeability coefficient surface area product for the residual plasma volume. This action is consumed by leptin in the vessel bed of different brain regions. The transport of leptin into the central nervous system represents a crucial step in the regulation of food intake and energy balance. Obese rats and high fat diet-induced obese rats have a deficit in leptin access into the brain through the blood-brain barrier. This fact indicates a cause for their obesity. Leptin levels in lean individuals are
already near saturation levels at the blood-brain barrier; therefore, leptin levels measured in obesity may not have biological effects because the system is already saturated (Burguera et al., 2000).

The specific leptin receptor (OB-R) allows leptin access through capillary walls to specific hypothalamic nuclei, as well as other areas in the brain, in order to exert its effects. This leptin receptor in the blood-brain barrier is easily saturated; the reduction of leptin uptake in obese rats is due to the increase of competition and resistance of endogenous leptin. When compared to cerebrospinal fluid levels of leptin, plasma leptin levels are much higher in obese individuals. The lack of leptin access to the brain could be responsible for obesity. The plasma concentration of leptin in lean individuals does not have such competition or decreasing leptin transport through the blood-brain barrier (Burguera et al., 2000).

Hyperleptinemia is a form of obesity caused by naturally high levels of leptin. Higher leptin receptor levels at the blood-brain barrier in response to high-caloric intake could be a physiological response to allow increased leptin access to specific hypothalamic/pituitary areas associated with growth and reproduction. The decreasing permeability at the blood-brain barrier might be secondary to the higher levels of circulating leptin in obese groups. The leptin receptor is involved in the regulation of leptin availability to brain cells. Its functions are limited due to saturation because of hyperleptinemia. This study agrees with the conclusion that the presence of saturable transport mechanisms in the blood-brain barrier and explains why obesity is caused by a significant increase in plasma leptin levels (Burguera et al., 2000).
High fat meals increase circulating levels of neurotensin in the human body. Neurotensin is a peptide active in the hypothalamus and the intestine called N-cells. These N-cells in the intestinal tract are able to sample contents of fat in the lumen and secrete neurotensin for immediate circulation. Fat is most likely the primary nutrient that causes stimulation for neurotensin release and is recognized in the lumen of the intestine by N-cells. Direct lipid instillation into the duodenum is a way to compare the rise of neurotensin levels after meals. When comparing these neurotensin levels after meals and after direct injection of fat, it is found that neurotensin levels only increase modestly after normal meals. The increase is significantly greater when fat is injected directly into the duodenal lumen. The physiologic effects of neurotensin secreted from the intestines may be exerted in a paracrine fashion or inside the hepatic-portal circulation of humans (Ferris et al., 1990).

The conclusion is that when excessive amount of fats are consumed by fasting subjects, levels of neurotensin rise, but only modestly. From this, is it speculated that changes in the physiology of the gut can account for the lipid-stimulated release of neurotensin. Examples of these changes include a decrease in gastric acid secretion, gastric motility, and an increase in the blood flow to adipose tissue. Also, an increase in pancreatic exocrine secretion can be initiated by the intravenous administration of neurotensin after ingestion of lipid (Ferris et al., 1990).

The administration of naloxone, an opiate receptor antagonist, was designed to modulate postprandial levels of insulin, glucagons, pancreatic polypeptide, somatostatin-like immunoreactivity, and gastrin in response to carbohydrate and fat-rich meals. The study by Schusdziarra et al. (1983) displayed an effect from naloxone on all of these
except gastrin levels. It was shown that when the fat-rich meal was ingested alone, endogenous opiates have either no effect or a stimulatory effect except for the release of late inhibitory glucagons. This suggests that endogenous opiate receptors and opiates participate in the regulation of these functions in the gastrointestinal tract (Schusdziarra et al., 1983).

Postprandial (occurring after a meal) haemostasis and dietary fatty acids interact with each other in such a way that dietary lipids are able to modify haemostatic function long term, after dietary intervention, and acutely after a meal. When natural low fat foodstuffs are supplemented with triglycerides (defined fatty acid contents), it is possible that subjects may be able to determine the absorption of fat efficiently enough to recognize changes in haemostatic variables known to occur with high-fat ingested meals. Defined fatty acid content was used in order to mimic levels in which a normal response would be induced. Also, the possible influence of fatty acid position within the triglyceride molecule and its absorption and metabolic effects was investigated. This study illustrated that physiologically sized meals with distinct fatty acid compositions do not alter haemostatic variables. The cause of this is most likely due to that fact that the proportions of individual fatty acids were altered by the processes of digestion. Absorption and secretion were also associated with the formation of chylomicrons (Hunter et al., 1998).

Leptin was shown again and again to have the ability to regulate food intake and energy balance. Leptin levels are easily saturated at its receptor at the blood-brain barrier and its amounts can be reduced through expression of specific genes. With regard to the physiological responses of fatty acids, insulin and glucose play important roles in the
metabolism of mammals and humans. Orlistat was shown not to have significant affects on increasing caloric intake or reducing the feelings of satiety. Rising levels of neurotensin caused by increasing fat in a diet affects the body in a negative manner. Finally, when natural foodstuffs are supplemented with triglycerides with normal fatty acid content, the absorption of fat can measure changes in haemostatic variables known to occur with high fat meals.

Section III: Neurological Effects

Many areas of the brain are shown to be involved in feeding behaviors and to regulate the amount of food ingested during a meal. Depending on the character of their neuronal discharge, neurons in the hypothalamus and the amygdala play a role in hunger and satiation. The hypothalamus and the paraventricular nucleus both modulate activity of gut sensitive neurons thought to elicit a change in feeding behaviors. Another important area of the brain is the medial hypothalamus. Lesions in this area lead to overeating and obesity. The lateral hypothalamus controls neurotransmitters that act on food ingestion and feeding behaviors. Besides areas of the brain, people may have distinct phenotypes which would lead them to have different responses to energy and nutrient challenges.

Peptides, leptin, brain insulin, and neurotransmitters are also known to play a role in feeding also. Peptides in the parabrachial nucleus have been studied to determine if their function regulates food intake or whether peptides contain opioids that promote feeding in other areas of the brain. One such peptide is bombesin. Bombesin acts on the caudal hindbrain and is thought to suppress feeding when administered. Leptin interacts with regions of the brain, as well as in the gut; where it activates in the brain is not
certain. The nucleus of the solitary tracts’ role in feeding is illustrated as lesions ease the suppression of food intake when CCK is administered. CCK also increases levels of norepinephrine that suppress catecholamine release when administered to the paraventricular nucleus or ventral medial nucleus. c-Fos has indicated that the nucleus of the solitary tract and area postrema are also related to feeding behavior by marking these areas when excitation occurs. Brain insulin has a negative effect on food intake and reduces eating.

Hypothalamic and amygdalar neurons play a role in the state of food motivation. In the transition from hunger to satiation, the character of a single neuronal impulsation of hypothalamus and amygdala change in different ways. One way it changes is that a greater number of hypothalamic neurons, compared to amygdalar, change their discharge frequency. Also, during hunger, the number of hypothalamic neurons decrease and amygdalar increase. The strongest changes in neuronal discharge are seen in the left hypothalamus and amygdale. The largest difference between the left and right hypothalamus is during the state of hunger, and between the left and right amygdale occurs after satiation (Pavlova, 2003).

The hypothalamus is known to affect endocrine and autonomic function from its interactions with the pituitary. When lesions occur in the lateral hypothalamus (LH) there is a reduction in vagal nerve activity. This action indicates its importance with gastric acid secretion, glucose utilization, and gastrointestinal motility (Zhang, 1999). The paraventricular nucleus (PVN), upon stimulation, modulates the activity of gut-sensitive neurons on the dorsal motor nucleus of the vagus nerve (DMVN), as well as the nucleus of the solitary tract (NST) (Zhang, 1999). The DMVN houses gut-sensitive
neurons and most are excited by PVN stimulation. One function of the PVN is to adjust the processing of visceral and gustatory afferent information through the NST (Kirchgessner & Sclafani, 1988). The gut-sensitive neurons in the NST are thought to inhibit DMNV. The descending pathway of the PVN results in the inhibition and excitation of gastrointestinal function and plays a role in feeding behaviors (Zhang, 1999).

Peptides that regulate food intake in the parabrachial nucleus (PBN) regulate ingestion and contain opioids that promote feeding in other areas of the brain. This has been tested through examining actions of opioid receptor agonist DAMGO when injected into the lateral PBN. This action increased food intake; whereas, naloxone and opioid receptor antagonist, CTAP, decreased food intake. The decrease in food intake simulated hypophagia occurred when opioid pathways are highly activated. The PBN is therefore thought to mediate neurotransmission that recognizes aversive stimuli and is generated by opiate stimulation in the gut. This provides support for the PBN as a locus in the brain where opioids subserve as the distributed neural network and adjusts for normal feeding behavior (Wilson et al., 2003).

Bombesin acts on the caudal hindbrain to suppress feeding and produces reactions similar to satiety when administered peripherally and centrally. Ladenheim & Ritter (1993) created lesions to destroy the AP and NST noting the high concentrations of bombesin peptide and the high-affinity binding site for bombesin in these areas. The aim was to investigate bombesins’ participation on feeding. Therefore, lesions made to one or both of these areas in the brain caused the animal subjects to eat significantly more than the control group after BBS was administered. Lesions in which both the AP and
NST had extensive damage completely took away food suppression with high and low doses of bombesin. If lesions were limited to the AP, only suppressions are seen with low doses and not high doses. This indicates that the NST is the primary area that mediates the suppression of food intake and has a higher affinity of binding sites when bombesin is administered (Ladenheim & R.C. Ritter, 1993).

Lesions in the NST also ease the suppression of food intake when CCK is administered, but has no effect when lesions are made to the AP. The findings of lesions that calm CCK-induced suppression of food intake also are found to reduce bombesin-induced suppression of feeding. This suggests that peripherally administered CCK and bombesin may act to suppress feeding through a common neural substrate. Such common neural substrates could be classified as gastric vagal neurons (Ladenheim & Ritter, 1993). Over eating is caused when a neurotoxin, such as capsaicin, is injected into the AP and NST. This indicated that more than one neural population is damaged with lesions to these areas (South & Ritter, 1983).

A relationship between putative satiety peptides and endogenous norepinephrine exists in the hypothalamus. When CCK is added to the PVN or VMN of a satiated rat, norepinephrine levels increase. Norepinephrine levels increase without affecting the rats’ amine activity, but they suppress catecholamine release (Myers et al., 1986). Catecholamines play several roles in the central control of feeding with their presence endogenously across and through the midline of the hypothalamus. Also, the application of catecholamine agonists induce spontaneous feeding which can be suppressed by blocking agents. Furthermore a lesion in the brainstem pathway depletes forebrain catecholamines causing interference with the regulation of food intake (Myers et al.,
Also, a lesion produced from a neurotoxin into catecolaminergic pathways, hypothalamus, or cerebral ventricle impairs ingestive behavior. Food deprivation influences the content of norepinephrine absorption in the hypothalamus, as well as, dopamine and norepinephrine synthesis and turnover (Myers et al., 1986).

Finally, during ingestive behavior, norepinephrine and dopamine are released from certain areas of the hypothalamus. Norepinephrine is a catecholamine of the sympathetic nervous system and dopamine is its precursor. Besides catecholamines and CCK, GABA and other amino acids, serotonin (5-HT), free fatty acids, acetylcholine, prostaglandins, bombesin, calcium ions, calmodulin, calcitonin, and NPY play important roles in the central control of feeding (Myers et al., 1986). GABA is one of the most important inhibitors of the central nervous system and acetylcholine is a polypeptide component of insulin. Serotonin, NPY, and calcium ions function as neurotransmitters. Prostaglandins are compounds derived from unsaturated fatty acids that interact with free fatty acids in the plasma. Calmodulin is a calcium binding protein while calcitonin is a polypeptide hormone produced by the thyroid that causes a reduction of calcium ions in the blood. All of these form an intricate system in which the role of feeding is regulated. From this information, it is perceived that CCK or other retroactive peptides could serve as a “neuromodulator” of the pre-synaptic release of norepinephrine within hypothalamic structures thought to cause both hunger and satiety (Myers et al., 1986).

Overeating is also a consequence of lesions in the medial hypothalamus (MH); lesions in the MH are responsible for hyperphagia and obesity due to the damage to a fiber pathway lateral to the VMN that inhibits feeding. This pathway runs through the PVN; when this area is damaged, overeating occurs. The fibers of the pathway run
longitudinally in the ventral pontine and medullary reticular formation before projecting dorsomedially to the NST/DMVN where they terminate (Kirchgessner & Sclafani, 1988).

The lateral hypothalamus (LH) is a critical component of the brain mechanisms that control behaviors such as eating, sleeping, and drinking. The LH has connections with the forebrain, brainstem, and spinal cord that give the LH the ability to combine or change neurophysiological signals under its control. One control is performed by neurotransmitters in the LH, such as glutamate, and it is important for the organization of feeding and body weight regulation. Glutamate, an excitatory neurotransmitter, elicits feeding in satiated rats when the LH is excited or when injected directly into the LH. Opposing forces to the LH are NMDA receptor antagonists that suppress feeding and body weight. It has been found that glutamate and NMDA receptors in the LH may have important roles in mediating feeding and body weight. There is also an interconnected reward circuit between the LH, nucleus of accumbens, and ventral tegmental area that influences reinforcing behaviors for feeding, drug use, and self stimulation (Duva et al., 2005).

An early gene product that signifies neural activation, c-Fos, is prominent in the NST and AP of satiated rats but low in rats that ate a rationed meal or no meal. C-Fos is a marker of stimulus-induced neural activation; thus, illustrating that the NST and AP are areas of the brain in which food ingestion causes stimulation. This signifies that c-Fos is connected with the role of feeding in the NST and AP. Gastric distention also contributes to the promotion of satiety to food ingestion by activating vagal mechanoreceptors that excite the dorsal vagal complex in the NST and AP. When the AP is lesioned, rats consume the normal amount of food but eat much more at an individual feeding than
normal rats. This suggests that the AP is an important area of the brain for detecting early inhibitory signals accompanied with food ingestion. There is a direct proportional relationship between gastric distention and vagal mechanoreceptor activation. When the amount of distention is increased, it is combined with increasing firing rates of individual mechanoreceptors and additional recruitment of units. In a study conducted by Rinaman et al. (1998), the postmortem weight of gastric contents and the proportion of NST catecholaminergic neurons expressing c-Fos were in positive correlation. The results indicate that there is evidence for a direct and proportional link between the physiological or pharmacological stimulation of gastric vagal mechanoreceptor contributions to catecholaminergic NST neurons and inhibition of feeding behavior (Rinaman et al., 1998).

Leptin is already known to affect food intake, but where leptin activates in the brain is not certain. Leptin administered to the third ventricle caused the satiety actions of CCK to increase the suppression of food intake produced by CCK. The leptin-CCK combination also results in increased c-Fos activation in the PVN of the hypothalamus. The combination produced higher levels that the activation produced by leptin alone. This suggests the actions of leptin on food intake depend on its ability to respond as a within-meal satiety signal. Leptins actions on food intake stem from interactions with the arcuate nucleus that extend to the PVN. In the PVN, both NPY and melanocortin have roles in mediating the actions of leptin through this pathway (Emond et al., 1999).

Insulin in the CNS and is related to energy homeostasis. Brain insulin (found both in the CNS and peripherally) has a negative effect on food intake. The ingestion of nutrients triggers a sequence of neurochemical events that signal the CNS. This sequence
down regulates stimulators, activates anorexigenic factors (brain insulin), and causes reduced eating (Gerozissis, 2004). With an impairment of brain insulin, obesity and diabetes are likely to occur since brain insulin induces both short and long term effects on food intake regulation and body weight. Insulin acts as a mediator between the peripheral endocrine system and the brain through various steps of the neuroendocrine axis. The hippocampus is involved with detection and utilization of hunger and satiety signals and memory of food intake. This is revealed as the animals are fed at the same time each day because their body synthesizes and secretes hormones (insulin) that regulate food intake to prepare for the meal (Gerozissis, 2004). Insulin levels rise as the rats’ bodies prepare for the coming meal in order to begin the digestive process that will come after food is ingested. This process suggests that brain insulin is a potential neuromodulator involved in cognitive processes related to feeding and the memory of meals presented (Gerozissis, 2004).

Lastly, the notion that low-fat and high-fat consumers may have distinct phenotypes that lead them to have different responses to energy and nutrient challenges was recently addressed. The study by Cooling and Blundell (1997) measures satiation and satiety through specific intake of fat in a meal presented to the subjects. The meals contain either a low fat or high fat meal for lunch. Afterwards, the subjects record their intensity of hunger between the high fat and low fat meals. The results found that sensory and metabolic processes underlying satiation and satiety operate differently in individuals who consistently eat diets varying in the proportion of fatty foods. There are emerging patterns of responses that indicate a relationship between diet and obesity.
Therefore, these two groups are able to be distinguished as distinct phenotypes both behaviorally and physiologically (Cooling & Blundell, 1997).

The areas of the brain that have been shown to be involved in feeding behaviors and to regulate the amount of food ingested during a meal are the hypothalamus, AP, PBN, NST, PVN, and DMVN. In both the medial and lateral hypothalamus, hunger was reduced after feeding and lesions of these areas caused an increase in overeating. Excitation and inhibition occur in the descending pathway of the PVN to play a role in feeding behaviors. The NST indicates that it is the primary area that mediates the suppression of food intake and lesions of the NST reduce the suppression of food intake. CCK was one of the many things shown to act on areas of the brain to inhibit or excite their function. Besides areas of the brain, people may have distinct phenotypes that lead them to have different responses to energy and nutrient challenges.

**Conclusions:**

There are many exciting aspects in obesity research that give hope to reduce this avoidable disease. Reducing the number of fat cells through conjugated linoleic acid in adipose tissue, instead of reducing cell size, would be beneficial for decreasing weight in obese individuals. If both number and size of cells were decreased a better outcome would be demonstrated. The decrease in cell size has only been seen in lean individuals; a way in which this effect of conjugated linoleic acid could be seen in obese individuals needs to be further researched. A way in which this could be done is to possibly reduce the amount of long-chain fatty acids or saturated fatty acids found in foods. Reducing the fatty acids that cannot be absorbed as readily as medium-chain fatty acids or unsaturated
fatty acids would be a small step to reducing the total number of fat cells accumulated in adipose tissue.

Conjugated linoleic acid has been extensively studied for its interactions with fat. Conjugated linoleic acid decreases body fat mass and occur naturally in dairy products. An interesting study could be conducted by the addition of conjugated linoleic acid to foods. This could increase the reduction on fat mass in the body. However, when conjugated linoleic acid is combined with oils, there is an increase in adipose tissue weight. To find a way in which conjugated linoleic acid and oils could interact and not increase fat mass would be a major breakthrough in research for decreasing obesity.

One way in which society has already begun to increase the amount of healthy foods to help with obesity is the availability of soy products. Soy protein stimulates fatty acid oxidation and enhances ones body-fat reducing potential. There are many food products made from soy or has soy in it to replace the more fatty foods. Having more healthy foods available to the public is a good step to making people more knowledgeable about problems with obesity.

Leptin, insulin, and glucose are all components that act on the brain to induce or suppress food intake. Even though many studies have been done that involve all of these components, more research still needs to take place. Knowing the ways in which these components affect the body is the first step and learning how to control them is the next step. Keeping leptin level in the body is important so overeating does not occur. To find a way that the leptin receptors at the blood-brain barrier can increase its level of saturation will be an important find. Also, problems with insulin and glucose are seen in obese people, but a cure has not been discovered.
Subjects that have impairments in areas of the brain, such as the area postrema, nucleus of the solitary tract, hypothalamus (medial and lateral), dorsal medial vagal nucleus, paraventricular nucleus, and amygdala are affected with abnormalities like feelings of hunger and satiety. Usually abnormalities with feelings of hunger and satiety coincide with obesity. Much information is known about the brain and the regions in which feeding is regulated, but results between individuals may vary. This signifies the fact that areas of the brain known to affect feeding, hunger, and satiety are not clear. There are still grey areas about how different peptides, neurotransmitters, and other components affect the areas of the brain.

Although much is already known about the influence of dietary fat on the digestive system and how areas of the brain are affected that is involved in feeding and reinforcement, there are still unknowns that need to be addressed. From further research, exact areas of the brain and the neurons, peptides, neurotransmitters, etc that affect it can be identified. Such knowledge will be able to impact society and the problems associated with high fat foods.
References:


