Fast Food, Central Nervous System Insulin Resistance, and Obesity

Elvira Isganaitis, Robert H. Lustig

Abstract—Rates of obesity and insulin resistance have climbed sharply over the past 30 years. These epidemics are temporally related to a dramatic rise in consumption of fast food; until recently, it was not known whether the fast food was driving the obesity, or vice versa. We review the unique properties of fast food that make it the ideal obesigenic foodstuff, and elucidate the mechanisms by which fast food intake contributes to obesity, emphasizing its effects on energy metabolism and on the central regulation of appetite. After examining the epidemiology of fast food consumption, obesity, and insulin resistance, we review insulin’s role in the central nervous system’s (CNS) regulation of energy balance, and demonstrate the role of CNS insulin resistance as a cause of leptin resistance and in the promotion of the pleasurable or “hedonic” responses to food. Finally, we analyze the characteristics of fast food, including high-energy density, high fat, high fructose, low fiber, and low dairy intake, which favor the development of CNS insulin resistance and obesity. (Arterioscler Thromb Vasc Biol. 2005;25:2451-2462.)

Key Words: fast food ■ insulin ■ leptin resistance ■ nucleus accumbens ■ obesity

Fast food, defined by the United States Department of Agriculture (USDA) as “food purchased in self-service or carry-out eating places without wait service” has exploded in popularity since its humble origins in the roadside hamburger stands of 1930s California. There are now >240,000 fast food restaurants in the United States. Fast food is available in schools, offices, airports, and hospitals across the US and around the world. Fast food tends to be high in fat, energy-dense, poor in micronutrients, and low in fiber. Consequently, literature in the scientific and mainstream press (eg, “Fast Food Nation,” “Supersize Me”) is beginning to scrutinize fast food’s impact on public health. The verdict is harsh: evidence implicates fast food as one of the major causes of obesity, rates of which have risen sharply over the past 30 years.

The current obesity epidemic is well documented. The prevalence of obesity is rising across all demographic and age groups. Obesity stems from a positive mismatch between energy intake and energy expenditure. Western societies are “obesigenic” environments where people have become sedentary while food portions have grown “super-sized” and highly processed convenience foods and soft drinks provide a glut of calories throughout the day.

The twin epidemics of fast food consumption and obesity are intimately linked. We review the specific mechanisms whereby fast food contributes to the development of obesity. We posit that fast food, through its effects on insulin homeostasis, adversely impacts the neuroendocrine regulation of energy balance and plays a key causal role in the pathogenesis of obesity.

Linking Fast Food to Obesity

Trends in Obesity

Obesity has reached epidemic proportions in the US and worldwide. According to National Health and Nutrition Examination Survey (NHANES) data, in 1999 to 2000 31% of US adults were obese (ie, body mass index [BMI] >30), a marked increase from 13% in 1960 to 1962. For children, rates of obesity have risen even faster; in 1963 to 1965, only 4.2% of children aged 6 to 11 were obese (ie, BMI >95th percentile for age), by 1999 to 2000 that rate had more than
tripled to 15.8%. Whereas the increase in BMI is occurring across age ranges and among all ethnic groups in the US, the increase has been most notable among black, Latino, and Native American groups. Other developed and developing countries are keeping pace.

The increase in prevalence and severity of obesity has occurred too fast to attribute solely to genetics. Modeling trends in BMI distribution from the 1960s into the 2000s suggest that the entire curve has shifted, not just the tail end. Thus, environmental factors must be implicated, and whatever is happening, is happening to everyone.

Trends in Fast Food Intake
Fast food comprises a growing portion of food eaten outside the home. In 1953, fast food accounted for 4% of total sales of food outside the home; by 1997, it accounted for 34%. As a percentage of discretionary food expenditure, fast food doubled from 20% in the 1970s to 40% by 1995. Finally, as a percentage of total energy intake, fast food quintupled from 2% in the 1970s to 10% in 1995. One-third of US adults report having eaten at a fast food outlet on any given day; 7% of Americans eat at a fast food restaurant daily.

Trends in Sugared Beverage Intake
Sugared beverage consumption has increased markedly over the past 3 decades. Between 1977 and 1996, the proportion of individuals consuming sugared beverages increased (from 61.4% to 76%), frequency of consumption increased (from 1.96 to 2.39 servings per day), and portion size increased (from 13.6 to 21 oz/d). Average total calories from sweetened beverages more than doubled, from 70 kcal to 189 kcal per day. Between 1977 and 1996, soft drink consumption climbed by 70% for 2- to 18-year-olds, and by 83% for 19- to 36-year-olds. Sugared beverage intake has partly replaced dairy beverage intake in children and teenagers—as sugared beverage rose, milk consumption dropped by 38% since 1971. After the home, fast food restaurants are the second most common place where sweetened beverages are consumed. Soft drinks are a leading source of carbohydrates for most common place where sweetened beverages are consumed. After the home, fast food restaurants are the second most common place where sweetened beverages are consumed. Soft drinks are a leading source of carbohydrates for most

Connections Between Fast Food and Obesity
Nutritional analysis shows fast food to be high in fat, saturated fat, energy density, fructose, and glycemic index, yet poor in fiber, vitamins A and C, and calcium. A typical fast food meal contains 1400 kcal, 85% of recommended daily fat intake, 73% of recommended saturated fat, but only 40% of recommended fiber and 30% of recommended calcium. Fast food’s macronutrient composition, its large portion sizes, and its frequent pairing with equally large portions of sugar-sweetened soft drinks contribute to excessive energy intake. For example, children who eat fast food consume more total energy (187 kcal) daily than those who do not.

Observational cross-sectional studies have repeatedly linked fast food to obesity and to insulin resistance. Adults who report eating fast food have higher mean BMI than those who do not, even when demographic variables are taken into account. In a prospective study of fast food habits, baseline fast food intake correlated with obesity; increases in fast food intake were associated with increases in BMI and development of insulin resistance, even after controlling for demographics and macronutrient composition. In this same study, individuals with >2 visits to fast food restaurants per week gained 4.5 kg over 15 years and were more likely to become insulin resistant. In a second prospective trial, an increase in frequency of fast food restaurant use by 1 meal per week was associated with an increase in body weight of 1.6 lb above the 3.7 lb average weight gain over a 3-year study period.

A second epidemiological link between fast food and obesity can be drawn by examining studies of sugared beverage consumption. As mentioned, soft drinks frequently accompany fast food meals. Sugared drink consumption increases the risk of obesity among pre-school children and older children, and increases risk of obesity and type 2 diabetes mellitus (T2DM) in adults. In a study of 6th and 7th graders, every daily portion of sugared drinks led to a 60% increase in relative risk of obesity. The inverse also appears to be true, because studies aiming to decrease sugared-drink consumption in school-aged children have proven effective in reducing the prevalence of obesity.

Linking Obesity to CNS Insulin Resistance

Trends in Insulin Resistance
T2DM is characterized by peripheral insulin resistance, with eventual β-cell failure. Prevalence of T2DM has more than doubled between 1980 and 2002, and it is projected to double again by 2050. Meanwhile, T2DM prevalence has increased almost 10-fold in the pediatric population, now accounting for 30% of new diabetes diagnoses in 11- to 18-year-olds. Obesity and T2DM are inexorably linked, because 46% of adults with T2DM have a BMI >30 kg/m², and an even greater proportion are overweight.

Insulin resistance is thought to underpin the metabolic syndrome, which has been defined as 3 of the 5 following criteria: abdominal obesity, hypertriglyceridemia, low high-density lipoprotein, hypertension, and high fasting glucose (NCEP ATP III definition). Metabolic syndrome is estimated to affect 20% to 25% of the US adult population.

Relation of Insulin Dynamics to Obesity
The causal links between obesity and insulin resistance are complex and controversial. Experimental and clinical studies are gradually painting a picture in which obesity promotes insulin resistance, and insulin resistance conversely facilitates further weight gain.

Obesity as a Cause of Insulin Resistance
Obesity is central to the development of insulin resistance. Risk of insulin resistance escalates with increasing obesity. Moreover, weight gain from overfeeding induces insulin resistance, whereas weight loss by calorie restriction reverses insulin resistance. Free fatty acids (FFAs) may be
one of the mechanisms linking the 2 entities—high circulating levels of FFAs released from adipocytes promote insulin resistance in liver and muscle, in a phenomenon known as “lipotoxicity.” The adipose tissue derived hormone adiponectin, which increases insulin sensitivity, is a second connection between obesity and insulin resistance. Obese individuals secrete less adiponectin than lean individuals; weight loss restores adiponectin to normal levels. The adipocyte-derived hormone resistin has also been implicated in causing insulin resistance in hepatic tissue. Other putative mechanisms through which obesity may cause insulin resistance stem from the discovery that fat tissue is immunologically active. Adipocytes secrete several cytokines (tumor necrosis factor-α, IL-6, IL-1β, etc) that induce insulin resistance and correlate with the metabolic syndrome.

**Insulin Hypersecretion and Insulin Resistance as Causes of Obesity**

Insulin is the primary hormonal signal for energy storage into adipocytes. Insulin hypersecretion by the pancreas plays a role in the pathogenesis of some forms of obesity. For example, infants of diabetic mothers tend to be large for gestational age, and initiation of insulin therapy in diabetes pregnancy is associated with weight gain. The phenomenon of hypothalamic obesity, characterized by vagally mediated insulin hypersecretion provides further evidence for the obesigenic properties of insulin excess. In natural history studies, infants who hypersecreted insulin in response to an intravenous glucose tolerance test gained excess weight over a 15-year follow-up period, analogously, fasting hyperinsulinemia predicted weight gain over 9 years in a group of Pima Indian children, independent of baseline BMI.

Because insulin resistance and hypersecretion often coexist and are partly interdependent, it can be difficult to tease out the relative contributions of each to the genesis of obesity. Still, insulin resistance appears to contribute to weight gain in adults and children, particularly with regard to the development of abdominal obesity. This may occur because of heterogeneity in insulin resistance between tissues. Adipose tissue tends to retain its sensitivity to insulin in the face of hepatic and skeletal muscle resistance. In experimental models, adipose tissue-specific and muscle insulin receptor knockout animals remain lean, whereas liver and CNS knockout animals become obese and have type 2 diabetes develop. Chronic insulin administration leads to muscle insulin resistance, whereas adipose insulin sensitivity remains high.

Certain ethnic groups are particularly prone to both insulin resistance and obesity. For instance, Pima Indian and black children have been demonstrated to be insulin resistant in childhood, predating the onset of overweight. South Asian Indians born in India were found to weigh less at birth than their UK-born counterparts, but they have greater adiposity and higher insulin levels. Prenatal events may also set the stage for insulin resistance in later childhood. Newborns who have experienced intrauterine stress, are small or large for gestational age, or are twins have all been shown to have insulin resistance in later life, a variable predisposition to obesity, and an increased risk of metabolic syndrome. One postulated explanation for the ability of insulin resistance to cause obesity is the “thrifty phenotype” hypothesis, which holds that to survive periods of scarcity, human metabolism is “programmed” to store nutrients maximally in times of abundance. Humans have arguably never known such energy abundance as our current fast food culture.

Despite robust evidence linking insulin hypersecretion and resistance to obesity, the causal mechanism(s) are still being delineated. Insulin hypersecretion may alter glucose transport or downregulate insulin receptor expression. Conversely, insulin resistance in the liver and muscle may trigger compensatory increases in insulin secretion. It is still not clear whether insulin hypersecretion or resistance occurs first. One study of insulin dynamics among obese schoolchildren suggested that hypersecretion predates development of insulin resistance by several years. In rats, hyperinsulinemia increases expression of a glucose transporter (GLUT4) in adipose tissue while decreasing expression of this same transporter in muscle, demonstrating that excess insulin can simultaneously foster insulin sensitivity in fat while triggering resistance in other tissues. The relative contribution of insulin sensitivity versus resistance in obesity appears to differ among whites as compared with blacks.

**Neuroendocrine Regulation of Energy Balance**

The hypothalamus orchestrates the neuroendocrine control of energy balance in a complex neural loop that comprises:(1) afferent signals from the viscera and the CNS reflecting energy stores;(2) signal transduction in the periventricular nucleus and the lateral hypothalamic area; and (3) efferent signals to other parts of the hypothalamus, the limbic system, and the visceral organs that modify energy intake and energy expenditure (Figure 1). The ventromedial hypothalamus (VMH) receives afferent hormonal and neural signals related to energy balance, fat stores, and satiety. The main afferent signals include insulin, leptin, and several gut-derived hormones. Depending on the nutrient status, the VMH transduces either anorexigenic signals (eg, α-melanocyte stimulating hormone, cocaine-amphetamine-regulated transcript) or orexigenic signals (eg, neuropeptide Y and agouti-related protein). These are integrated in the paraventricular nucleus and lateral hypothalamus via the melanocortin-4 receptor, and to a lesser extent, the melanocortin-3 receptor. The major efferent pathways involve the sympathetic nervous system (SNS), which promotes energy expenditure, and the parasympathetic nervous system, which promotes energy storage. Insulin is part of both the afferent and efferent pathway; unraveling its dual role provides valuable insights into the pathogenesis of obesity.

**The Afferent Pathway**

**Alimentary Tract-Derived Afferent Signals**

Ghrelin, a 28-amino acid octanoylated peptide hormone first described in 1999, is now known to be an important afferent visceral signal in the control of feeding behavior. Ghrelin secretion by the “A-like cells” of the stomach increases during fasting, peaks at the moment of meal initiation, and declines after feeding. Ghrelin binds to the growth hormone secretagogue receptor in the hypothalamus to increase hunger
and food intake. In experimental animals, intracerebral administration of ghrelin increases feeding behavior, increases energy deposition in adipose tissue, and decreases fat oxidation. Serum levels of ghrelin in humans correlate with perceptions of hunger. Other gut-derived satiety signals include CCK, PYY3–36, GIP, and GLP-1.

Leptin as an Afferent Signal

Leptin first garnered recognition as the missing gene product in the ob/ob mouse and is now recognized as a key afferent signal in energy balance. Leptin is secreted by adipocytes in response to energy storage, under the control of insulin and glucocorticoids. Circulating leptin levels correlate with percent body fat and thus transmit information to the hypothalamus regarding long-term energy stores. Acute changes in leptin reflect short-term changes in energy balance; leptin levels decrease precipitously within 12 hours of fasting, declining faster than body fat stores. Decreases in leptin are interpreted by the hypothalamus as “starvation,” eliciting an adaptive response that increases appetite and decreases resting energy expenditure (REE); conversely, increases in leptin curb food intake and increase SNS activity with resultant increased energy expenditure. Of note, leptin’s ability to suppress appetite plateaus when levels rise beyond a “leptin set-point;” leptin has been described as a signal with a floor but no ceiling. Exogenous leptin administration fails to trigger weight loss; thus, obesity has been characterized as a “leptin-resistant” state.

The leptin receptor is densely clustered on VMH neurons and is a member of the cytokine receptor family. Leptin amplifies short-term satiety signals such as POMC, CART, and inhibits neuropeptide Y. Leptin also curtails feeding behavior by modifying pleasurable, or “hedonic” responses to food; in this regard, and in many others, leptin is similar to insulin.

Insulin as an Afferent Signal

Insulin also plays a pivotal role in the control of appetite and feeding. In addition to its well-defined peripheral role in glucose clearance and utilization, insulin is involved in the afferent (and efferent) hypothalamic pathways governing energy intake, and in the limbic system’s control of pleasurable responses to food. Whereas insulin drives the accumulation of energy stores in liver, fat, and muscle, its role in the CNS tends to decrease energy intake. This is not a paradox, but rather an elegant instance of negative feedback. When energy stores abound, circulating insulin tends to be high; high CNS insulin tends to decrease feeding behaviors, thereby curtailing further accumulation of energy stores. Insulin’s central effects on energy intake are manifested in 2 complementary ways: first, insulin decreases the drive to eat; second, insulin decreases the pleasurable and motivating aspects of food.

Insulin’s CNS effects were first described in 1977, when Wood et al observed that intracerebroventricular infusion of insulin decreased feeding behavior in baboons. Later, with the discovery that pharmacological blockade of CNS insulin receptors causes hyperphagia and obesity in mice, and with the subsequent observation that the CNS-specific insulin receptor knockout mouse becomes obese, insulin gained recognition as a key neuronal signal in the control of energy balance. Insulin’s central effects include decreased feeding behavior, increased REE, and increased oxidative metabolism of fat. Interestingly, some of insulin’s effects on glucose metabolism are achieved through the CNS: blocking insulin signaling in the CNS has been shown to diminish peripheral insulin’s ability to suppress gluconeogenesis.

Insulin receptors are expressed throughout the CNS; the majority of these are located in the hypothalamus, olfactory bulb, hippocampus, and throughout the limbic system. Insulin is not synthesized in the CNS, but is transported there by a saturable transporter in the CNS capillary membrane. Although CNS insulin levels tend to reflect serum insulin levels, the relationship breaks down in obesity states. In obesity, there is proportionally less CNS insulin; the expression of the CNS insulin transporter is decreased in several obesity

---

Figure 1. Afferent (gray), central (black), and efferent (white) pathways in the regulation of energy balance. The hormones insulin, leptin, ghrelin, and PYY3–36 provide afferent information to the VMH regarding short-term energy metabolism and energy sufficiency. From there, the VMH elicits anorexigenic (α-MSH, CART) and orexigenic (neuropeptide Y, agouti-related protein) signals to the melanocortin-4 receptor in the paraventricular nucleus and lateral hypothalamus. These lead to efferent output via the dorsal motor nucleus, which activates the vagus nerve to store energy (in part by increasing insulin secretion), or via the LC, which activates the SNS, which promotes thermogenesis and lipolysis. (From Lippincott Williams & Wilkins, with permission.)
models. This paucity of insulin available for satiety signaling may represent a form of CNS insulin resistance.

**The Efferent Pathway**

The hypothalamus regulates energy storage and expenditure in part through its connections to the autonomic nervous system. The parasympathetic nervous system, through the vagus nerve, promotes energy storage, whereas SNS activation increases energy expenditure through lipolysis and thermogenesis.

**Vagal Efferent Pathway**

The parasympathetic system affects energy balance through signals projecting from the hypothalamus to the dorsal motor nucleus of the vagus, which in turn innervate the viscera, including the pancreatic β-cell. Vagal modulation of β-cell function promotes a stoichiometrically excessive insulin hypersecretion in response to a fixed glucose load. In both obese animals and humans, vagotomy promotes weight loss in part due to a reduction in the magnitude of insulin secretion.

**Peripheral Effects of Insulin (Efferent)**

Insulin is secreted by pancreatic β-cells in response to increases in serum glucose, although other substrates such as free fatty acids, ketone bodies, and certain amino acids can also directly stimulate insulin’s release or augment glucose’s ability to trigger insulin release. In the liver, insulin decreases glucose production (by inhibiting glycolgenolysis and gluconeogenesis) and increases the conversion of glucose into glycogen. In adipose tissue, insulin stimulates glucose uptake by the glucose transporter GLUT4. Although several other hormonal signals trigger lipolysis, insulin is the sole promoter of lipogenesis in the adipocyte. Insulin’s net effects are to decrease the amount of circulating glucose and to increase energy stores, most notably in the form of fat deposition.

**Sympathetic Efferent Pathway**

Cold, stress, and dietary changes modify the activity of projections from the paraventricular nucleus and the lateral hypothalamus, which lead to SNS activation, mediated by the locus coeruleus. SNS activation tends to mobilize energy stores by the following mechanisms: (1) increased circulating catecholamines stimulate glucagon secretion, which antagonizes insulin’s effects and indirectly inhibits insulin secretion; (2) thyroid-stimulating hormone increases thyroid hormone secretion and thyroxine-induced energy expenditure; (3) blood flow and oxygen consumption are increased in skeletal muscle; and (4) β-adrenergic receptors in white and brown adipose tissue increase thermogenesis and lipolysis.

**The Pivotal Role of CNS Insulin Resistance in Leptin Resistance and in Obesity**

**Overlap of Insulin and Leptin CNS Effects**

Throughout the CNS, insulin and leptin parallel one another’s effects. Both hormones are secreted during periods of energy sufficiency or excess, their receptors colocalize to the same VMH neurons, and both have similarly anorexigenic effects when administered into the cerebrospinal fluid (CSF). The redundancies in insulin and leptin’s effects allow one to conceive of them as dual barometers of energy stores; insulin levels reflect acute changes in energy intake, whereas leptin levels are an integration of energy stores over a longer period of time.

There tends to be a correlation between serum and CNS levels of insulin and leptin, but the relationship is not linear. In obesity, a state in which levels of circulating insulin are high, there is proportionally less insulin in the CNS. Leptin uptake into the CNS seems to follow a similar pattern to insulin, with low CNS leptin relative to serum leptin having been documented in several obesity models.

Obesity is a state in which the negative feedback pathways of insulin and leptin are ineffective: the CNS resists the regulatory effects of insulin and leptin, so that appetite remains uncurbed and weight accrues despite adequate energy stores. Despite high circulating levels of leptin and insulin in the setting of obesity, there is a paucity of CNS satiety signaling by these hormones, leading to an inappropriate perception of starvation. CNS insulin and leptin resistance are beginning to be understood, through mechanisms that are described below.

**Decreased CNS Transport**

The observation that leptin administered directly into the brain is more potent at curbing appetite in obese mice than peripherally administered leptin has led to speculation that leptin resistance is due to limited availability of the hormone in the CNS. Low CSF leptin levels have been documented in several rodent models of obesity. Leptin is transported into the CNS via a transporter expressed in brain vasculature; this transport is decreased in obesity. However, insensitivity to the behavioral effects of CSF insulin has been found in the insulin resistant obese Zucker rat, and also in lean rats that are fed a high-fat diet. Inadequate transport does not fully explain the CNS insulin resistance seen in obesity, but appears to be a contributing factor.

**Decreased Leptin Signaling**

Although insulin and leptin bind to separate receptors, they share the enzyme phosphatidyl inositol-3-kinase in their intracellular signaling cascades. Intracellular signaling by the leptin receptor is achieved through the JAK2/STAT3 pathway (Figure 2). Leptin’s ability to activate STAT3 in hypothalamic neurons is reduced when mice are fed high fat diets. SOCS3 and PTP1b are genes that have been shown to regulate leptin sensitivity; decreased expression (or knockout) of these genes enhances leptin sensitivity and gives rise to phenotypically lean mice. Studies of age-associated and dietary induced obesity suggest that SOCS3 expression is affected in these states, although data are not definitive. Insulin induces SOCS3, which then inhibits the insulin receptor and inactivates the leptin receptor by dephosphorylating the tyrosine 1138 residue.

**Insulin Reduction Improves Leptin Sensitivity**

Two paradigms have been shown to reverse leptin resistance in humans. First, weight loss in response to marked food restriction allowed exogenous administration of leptin to increase REE and thyroid levels back to baseline, permitting further weight loss. Second, suppression of insulin pharmacologically using the somatostatin analog octreotide led to...
weight loss and reduction of leptin levels, but did not decrease REE, suggesting an improvement in leptin sensitivity. Thus, insulin reduction (either through forced weight loss or pharmacological manipulation), reversed leptin resistance.

Hyperinsulinemia itself may be a cause of leptin resistance. As described, insulin and leptin use many of the same neurons, the same second messengers, and the same distal efferents to effect induction of satiety. In particular, both insulin and leptin receptors use the second messenger IRS2, a low abundance message. Its absence confers CNS insulin resistance and obesity. However, the role of IRS2 in the expression of leptin resistance is controversial. One study suggests that knockout of IRS2 in hypothalamic neurons promoted obesity and insulin resistance, and prevented leptin signal transduction, conferring a leptin resistant state; another study of IRS2 knockout shows similar effects on obesity, but maintenance of leptin sensitivity. It has moreover been shown that CNS insulin induces SOCS3, which inactivates the leptin receptor inhibits leptin signal transduction. Although confirmation in animal studies is needed, these data suggest that CNS insulin resistance may be a proximate cause of leptin resistance, promoting continued weight gain.

**Insulin, Leptin, and the Hedonic Value of Food**

Complementary to insulin and leptin’s ability to decrease feeding behavior, these hormones also appear to modify the “hedonic” (ie, pleasurable and motivating) responses to food. This would be desirable from a teleological standpoint, as both decreasing appetite and the pleasurable response to food would help curtail food intake in situations where energy stores are replete.

The limbic system, which comprises the striatum, amygdala, and specialized areas of the hypothalamus and hippocampus, forms the neural circuit that orchestrates motivation, pleasure and reward. Leptin and insulin receptors are expressed throughout the limbic system and both these hormones have been implicated in modulating rewarding responses to foods and other pleasurable stimuli. For instance, fasting and food restriction (when insulin and leptin levels are low) increase the addictive properties of drugs of abuse; intraventricular leptin can reverse these effects. In rodent models of addiction, food restriction increases addictive behavior, whereas CSF administration of either leptin or insulin decreases the addictive potential of a pleasurable stimulus. More specific to the pleasurable properties of food, leptin has been demonstrated to inhibit sweet-sensitive receptors on the tongue.

The striatal projections of dopamine neurons from the midbrain ventral tegmental area (VTA) to the nucleus accumbens are the limbic pathway that mediates the motivating, rewarding, and reinforcing properties of stimuli such as food, water, and addictive drugs. Pleasurable response from a food reward, measured by dopamine release from striatal neurons and dopamine receptor signaling, is greater in food-deprived rats than in those that fed freely. Both insulin and leptin receptors have been found on the dopaminergic neurons of the striatum. Insulin increases expression and activity of the dopamine transporter, which removes dopamine from the synapse; this is postulated to be a mechanism by which insulin blunts the pleasurable response to food. This hypothesis finds support in rat experiments where dopamine receptor antagonists and insulin act additively to acutely decrease the rewarding response to a palatable sucrose solution. Moreover, both leptin and insulin block rats’ ability to form a conditioned place preference association to a palatable food.

The VTA appears to mediate feeding on the basis of palatability rather than energy need. Stimulation of this area triggers feeding behavior in rats that have already been fed, provided they are given a palatable food. Acutely, insulin appears to inhibit the ability of VTA agonists (eg, opioids, DAMGO) to increase intake of palatable sucrose solutions in rat experiments.

In sum, CNS insulin and leptin play key roles in extinguishing the hedonic responses to food mediated by the
limbic system, the nucleus accumbens and the VTA. Hence, CNS insulin resistance may contribute to obesity by undermining the insulin-dependent neural mechanisms that normally blunt the pleasure derived from food in situations where energy stores are replete. CNS insulin resistance sets the stage for unchecked caloric intake in the face of positive energy balance, as evidenced experimentally by neuronal–insulin receptor knockout mice, who are hyperphagic and obese.25 By altering hedonic responses to food, CNS insulin resistance may drive excessive energy intake in a feedforward manner (Figure 3).

Linking Fast Food to CNS Insulin Resistance

Fast Food as an Energy-Dense Food

Energy density is defined as “the energy content per unit weight of food.”68 Fast food meals, typically high in fat, low in fiber, and accompanied by sweetened soft drinks, tend to have a high energy density. Although fast food accounts for 27% of eating occasions, it accounts for 34% of calories eaten. Prentice et al calculated the energy density of traditional African diets and compared it to the energy density of meals available at several large fast food chains. The traditional Gambian diet provides 439 kJ per 100 g, whereas energy density for fast food meals ranged between 1054 and 1167 kJ per 100 g.68

Energy density is linked to obesity via a number of mechanisms. First, energy-dense foods may interfere with appetite control mechanisms. Humans tend to ingest a similar bulk and weight of food day to day; consuming energy-dense foods drives daily caloric intake upward.69 Although individuals tend to decrease their immediate food intake after ingestion of fast food or other energy-dense meals, they do not compensate fully, leading to inadvertent overconsumption. Moreover, humans do not downregulate long-term energy intake to compensate for short-term energy-dense meals. In an illustrative experiment, adult volunteers were fed diets in which fat and energy density were covertly manipulated; when energy density was tripled, total energy intake increased by 50%, suggesting that there is some compensation for high energy density, but not enough compensation to keep daily energy intake constant.70 The ability of energy-dense foods to interfere with appetite regulation may be exaggerated in obese individuals. For instance, overweight adolescents were less able to decrease their energy intake and promote obesity.

Fast Food and Dietary Fat Intake

Fast food tends to be high in dietary fat.1 Although dietary fat is a strong predictor of weight gain,72 the relationship between dietary fat and carbohydrate appears to be more relevant than fat intake alone. Although diets that are both high in fat and low in carbohydrates (eg, Atkins) may attenuate the postprandial insulin response, the combination of both a fat load and a glycemic load appears to exaggerate the insulin response and promote further weight gain.73 With increasing obesity, the insulin response ultimately attenuates, possibly contributing to glucose intolerance.

Both animal models and observational studies in humans implicate high-fat diets in the development of insulin hypersecretion and insulin resistance.74 Insulin resistance and hyperinsulinemia are more closely linked to saturated than unsaturated fats. The ability of fatty acids to stimulate insulin secretion depends on their chain length, saturation, and cis/trans conformation.75 A diet rich in saturated fat is an independent predictor for high fasting and postprandial insulin concentrations.76 In humans, increases in dietary saturated fat are associated with increases in fasting insulin, postprandial insulin, and insulin secretion after OGTT. In a study of adult, nondiabetic twins, a 20 g/d increase in total dietary fat intake was associated with higher fasting insulin levels, even after controlling for obesity.77

In rats, glucose-stimulated insulin secretion is altered by fat intake, and by the composition of fat in the diet.78 Dietary fat composition not only impacts insulin secretion but also affects insulin sensitivity. Rats fed low-fat diets need a higher glucose infusion rate during clamp studies than those fed higher-fat diets. Activity of insulin-dependent PI-3-kinase in liver is decreased by high fat diets, suggesting a primary role for fat in hepatic insulin resistance.79 FFA may be the mechanistic link between high fat diets, insulin resistance, and insulin hypersecretion. In vitro and in vivo experiments have demonstrated that FFAs increase glucose-stimulated insulin secretion.78 Indeed, FFAs may be some circumstances be essential to insulin secretion; in fasted rats, lowering levels of circulating FFA using nicotinic acid eradicates the insulin response to a glucose load.80

High-fat diets may also contribute to weight gain via their effects on satiety signaling, in particular via CNS insulin and leptin.81 Mice fed high-fat diets have a decreased response to both peripheral and intracerebral infusions of leptin.51 In rats, a high-fat diet was shown to inhibit intracerebral insulin’s ability to decrease the drive for food.82 In women, high-fat meals, which produce smaller glucose and insulin responses than high-carbohydrate meals, reduce 24-hour leptin secretion.83

Fast Food and Glycemic Index and Load

Low-glycemic-index diets are increasingly recognized as potential modulators of obesity and insulin resistance. Yet with the increased popularity of highly processed foods, the glycemic load of the average American diet has been on the rise.84 Fast foods may be contributing to this increased glycemic burden. In general, fast foods contain more highly refined carbohydrates and less fiber than other foods, which inflates their glycemic index.

Glycemic index is defined as “the area under the glucose response curve after a carbohydrate-containing food is consumed, as compared with a control food (typically white bread or glucose).”85 The glycemic index of a food depends on the length of its polysaccharide chain, its fiber content, and its refined carbohydrate content. Glycemic load, defined as the “glycemic index of individual foods multiplied by the percent of dietary energy as carbohydrate,”85 is an indicator of global dietary insulin demand.
High-glycemic-index foods trigger greater postprandial elevations in serum glucose than low glycemic index foods, leading to a commensurate insulin secretion by \( \beta \)-cells. The resultant high insulin to glucagon ratio augments energy storage through lipogenesis and glycogenesis. The metabolic consequences of high-glycemic-index meals extend beyond the immediate postprandial period. High-glycemic-index meals are cleared quickly by the insulin response, yet the insulin surge continues to exert metabolic effects, often promoting a relative hypoglycemia 4 to 6 hours after a meal, which increases caloric intake at the next meal. In rats, high glycemic index feeds accelerate fat deposition and lead to obesity.\(^8^5\)

Short-term clinical studies link consumption of high-glycemic-index foods to increased energy intake. For example, obese children who ate high-glycemic-index meals subsequently consumed 53% more calories than children given low-glycemic-index meals with the same macronutrient composition.\(^6^6\) Single-day diet studies in adults show that high glycemic index meals are associated with decreased satiety, increased hunger, and increased voluntary food intake.\(^8^7\) Low-glycemic diets may impact energy balance not only through satiety and hunger but also by modifying resting energy expenditure. Whereas most weight loss regimens reach a plateau in their efficacy because of compensatory decreases in resting energy expenditure, low-glycemic load diets are associated with a smaller decline in REE than low-fat diets, suggesting they may be more efficacious for continued weight loss.\(^8^8\)

The glycemic index of a diet is linked not only to obesity but also to risk of T2DM. In a large prospective cohort study, the glycemic load of the diet was positively associated with risk for T2DM.\(^8^9\) High-glycemic-index diets may impair \( \beta \)-cell function via glucotoxicity, lipotoxicity, and overstimulation.\(^8^5\)

**Fast Food as a Source of Fructose**

The most commonly used sweetener in the US diet is sucrose (eg, table sugar), a disaccharide that contains 50% fructose and 50% glucose. In North America, non-diet soft drinks are usually sweetened with high-fructose corn syrup (HFCS), which contains up to 55% of the monosaccharide fructose. Because of its abundance, high relative sweetness, and affordability, HFCS has become the most common sweetener used in commercially produced foods. HFCS is found in processed foods ranging from soft drinks and candy bars, to crackers, ketchup, sauces, and even hamburger buns. According to USDA food disappearance data, average daily fructose consumption has increased by >25% over the past 30 years. Annual beet and cane sugar consumption decreased from 101.8 lb/capita in 1970 to 66.5 lb/capita in 1997, whereas HFCS intake increased from 0.5 lb/capita to 62.5 lb/capita in 1997.

The growing dependence on fructose in the Western diet may be fueling the obesity and T2DM epidemics. In a study of US adults, intake of corn syrup (a leading source of fructose) was positively associated with risk of T2DM, independent of total energy intake.\(^9^0\) There are few clinical trials evaluating the effects of fructose on weight gain in humans; several studies have demonstrated that excess fructose consumption contributes to weight gain over the short-term, but these have not controlled for calorie intake.\(^9^1\) There is, however, mounting evidence from animal models, in which high-fructose diets have been linked to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance. A recent study demonstrated that rats fed fructose increased their adiposity and insulin resistance without increasing their calorie intake.\(^9^2\) These data suggest that fructose consumption may be playing a role in the epidemics of insulin resistance and obesity.

The metabolism of fructose differs from that of other monosaccharides such as glucose in ways that modify insulin dynamics and obesity risk. Fructose is absorbed in the intestine by the transporter GLUT5. Glucose, which is frequently found in the same foods as fructose, enhances intestinal absorption of fructose.\(^9^3\) The GLUT5 receptor is expressed at low levels in muscle and adipose tissue, but the receptor’s most important site of action is the liver, where fructose is avidly absorbed from the portal circulation. There, fructose is converted to fructose-1-phosphate and enters the glycolytic pathway beyond the main regulatory step of glycolysis, phosphofructokinase. The enzymatic activity of phosphofructokinase responds to changes in glycogen stores and products of glycolysis (eg, citrate, ATP) and thus tightly regulates metabolism of glucose; fructose in contrast enters the glycolytic pathway unchecked. Fructose metabolism leads to an accumulation of intermediates of glycolysis that are converted to glyceraldehyde and acetyl-coenzyme A (CoA) before being synthesized into fatty acids, very-low-density lipoproteins, and triglycerides.\(^9^3\)

The effects of fructose on supplementary caloric intake and macronutrient preference remain controversial. Studies of acute fructose ingestion suggest an immediate short-term reduction in caloric intake.\(^9^4\) However, fructose ingestion has been shown not to suppress secretion of the so-called hunger hormone ghrelin, levels of which correlate with perceived hunger, perhaps because fructose fails to trigger a postprandial insulin rise.\(^9^5\) The lack of insulin secretion in response to fructose in turn reduces leptin production from adipose tissue, which negatively alters CNS perception of energy stores. In sum, fructose consumption has metabolic and hormonal consequences that may facilitate development of insulin resistance, leptin reduction, and obesity.

**Fast Food and Reduced Fiber Intake**

Fast foods tend to be low in fiber, which may be one of the characteristics that link it to obesity and insulin resistance. Cohort studies of young and middle-aged adults demonstrate that fiber intake is inversely associated with weight gain, fasting insulin levels, and risk of T2DM.\(^8^9\) Moreover, in a Swedish population study, dietary patterns characterized by high fiber intake were associated with a decreased incidence of certain features of the metabolic syndrome, including central obesity and hyperlipidemia.\(^9^6\)

Fiber intake may be mechanistically linked to obesity through its effects on glycemic index and energy density. Generally, high-fiber foods have low energy density and glycemic index (fiber content accounts for 50% of the variability in glycemic index between foods). But fiber may
also influence obesity risk through distinct hormonal and digestive mechanisms. High-fiber meals tend to be more satiating because they induce a greater sensation of fullness than low-fiber meals. In a meta-analysis of 27 experimental human studies on the effects of fiber intake on satiety, 17 studies supported a beneficial role for fiber in the regulation of energy intake.97 Fiber content also tends to add bulk and viscosity to meals, thereby slowing gastric emptying. Fiber-containing foods show slower glucose absorption, which lessens the postprandial insulin surge and may decrease lipogenesis. Moreover, the intestinal satiety signal cholecystokinin is augmented by high fiber meals, thereby contributing to central perception of satiety. Finally, because fiber-containing foods can escape digestion in the small intestine, their starches are susceptible to fermentation by colonic bacteria. The products of this fermentation process include short-chain fatty acids, which have been shown to decrease hepatic gluconeogenesis, and may alter insulin secretion patterns and improve insulin sensitivity.

Fast Food and Reduced Dairy Product Consumption
Fast food tends to contain less calcium than other foods.1 Emerging epidemiologic and clinical evidence is beginning to link calcium and dairy intake to risk of obesity and insulin resistance. It is still not clear whether these effects are mediated by calcium intake or by another attribute of dairy products.

Cross-sectional and experimental studies demonstrate a robust inverse correlation between calcium and dairy intake and obesity risk.98 A longitudinal study of dietary intake among young adults demonstrated that a high intake of dairy products was protective against the development of metabolic syndrome, even after controlling for demographic and nutritional factors such as race, age, gender, BMI, calorie intake, fruit and vegetable consumption, and dietary fiber.99 Experimental data in rodents and humans show that increasing dietary calcium during energy restriction accelerates weight loss, increases lean body mass and decreases adipose mass, as compared with calorie restriction alone.100 It has been suggested that dairy products are protective against obesity and insulin resistance because they are low-glycemic-index foods. High-calcium diets may also exert anti-obesity effects by increasing fecal fat excretion, particularly in response to high-fat diets. A third mechanism through which calcium and dairy products may be protective against obesity is mediated at the level of the adipocyte: high circulating calcium levels suppress circulating 1,25-dihydroxyvitamin D₃, which decreases intracellular calcium in the adipocyte and in turn reduces lipogenesis and augments lipolysis.

Summary
Dramatic increases in fast food consumption over the past 30 years have occurred in parallel with the twin epidemics of obesity and insulin resistance. Some of the properties of fast food, including its high glycemic index and its fatty acid composition, induce hyperinsulinemia and the development of insulin resistance, both peripherally (increasing energy deposition into fat), and centrally. Of course, fast food is merely the most extreme example of what has become the typical Western diet, so this phenomenon has implications for all patients with weight gain. Hyperinsulinemia is the primary initiator of CNS insulin resistance, which may in part be responsible for leptin resistance. This promotes reduced energy expenditure and continued food consumption in an attempt to make up for what the brain sees as an inadequate leptin level. Furthermore, CNS insulin resistance interferes with meal-associated insulin effects on dopamine reuptake and the extinguishing of the hedonic or reward system at the nucleus accumbens, which turns the pathway from a feedback into a feed-forward paradigm.

Acknowledgments
The authors thank Lee Ann Birch, PhD, Dennis Styne, MD, and Joanne Ikeda, RD, MPH for their constructive readings of this manuscript.
References


Isganaitis and Lustig


Fast Food, Central Nervous System Insulin Resistance, and Obesity
Elvira Isganaitis and Robert H. Lustig

Arterioscler Thromb Vasc Biol. 2005;25:2451-2462; originally published online September 15, 2005; doi: 10.1161/01.ATV.0000186208.06964.91
Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2005 American Heart Association, Inc. All rights reserved.
Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/25/12/2451

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Arteriosclerosis, Thrombosis, and Vascular Biology can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Arteriosclerosis, Thrombosis, and Vascular Biology is online at:
http://atvb.ahajournals.org/subscriptions/