Smart Life Forum

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Robert H. Lustig, M.D.

What's really behind the childhood obesity epidemic?

Cubberley Center, 4000 Middlefield Road, Room H1, Palo Alto

Thursday, January 18, 2007 at 7:00 PM

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MEET ROBERT LUSTIG

Robert H. Lustig, M.D. is currently Professor of Clinical Pediatrics in the Division of Endocrinology at University of California, San Francisco, and Director of the Weight Assessment for Teen and Child Health (WATCH) Program at UCSF.

Dr. Lustig is a neuroendocrinologist, with basic and clinical training relative to hypothalamic development, anatomy, and function. Prior to coming to San Francisco in 2001, he worked at St. Jude Children's Research Hospital in Memphis, TN. There, he was charged with the endocrine care of many children whose hypothalami had been damaged by brain tumors, or subsequent surgery, radiation, or chemotherapy. Many patients who survived became massively obese. Dr. Lustig theorized that hypothalamic damage led to the inability to sense the hormone leptin, which in turn, led to the starvation response. Since repairing the hypothalamus was not an option, he looked downstream, and noted that these patients had increased activity of the vagus nerve (a manifestation of starvation) which increased insulin secretion. By administering the insulin suppressive agent octreotide, he was able to get them to lose weight; but more remarkably, they started to exercise spontaneously. He then demonstrated the same phenomenon in obese adults without CNS lesions. The universality of these findings has enabled Dr. Lustig to weave these threads together into a novel unifying hypothesis regarding the etiology, prevention, and treatment of the current obesity epidemic.

A native of Brooklyn, NY, Dr. Lustig went to Stuyvesant H.S. in Manhattan, graduated from MIT in 1976, and received his M.D. from Cornell University Medical College in 1980. He completed his pediatric residency at St. Louis Children's Hospital in 1983, and his clinical fellowship at UCSF in 1984. From there, he spent six years as a post-doctoral fellow and research associate in neuroendocrinology at The Rockefeller University. He has been a faculty member at the University of Wisconsin-Madison, and the University of Tennessee, Memphis. Dr. Lustig has authored 60 peer-reviewed articles and 30 reviews. He has mentored 15 pediatric endocrine fellows, and trained numerous other allied health professionals. He provides endocrinologic support to several protocols of the Children's Oncology Group. He is the current Chairman of the *Ad hoc* Obesity Task Force of the Lawson Wilkins Pediatric Endocrine Society, a member of the Pediatric Obesity Practice Guidelines Subcommittee of The Endocrine Society, a member of the Obesity Task Force of the Endocrine Society, a member of the Pediatric Obesity Devices Committee of the U.S. Food and Drug Administration, and a member of the Steering Committee of the International Endocrine Alliance to Combat Obesity. He also consults for several childhood obesity advocacy groups.

Dr. Lustig lives in San Francisco with his wife and two daughters (ages 7 and 1). Spare time (what little there is) is spent cooking, theater-going, and traveling.

MAIN PRESENTATION

The big question: Who's to blame for our current childhood obesity and Type 2 diabetes (T2DM) epidemic? Depends on whom you ask. The Institute of Medicine says it's an interaction between genetics and environment. Well, our genetics hasn't changed in 30 years, but our environment sure has. The BMI distribution curve shows that all segments of the population are increasing in weight. The U.S. Government calls it a matter of "personal responsibility". How does the two year old population, who is witnessing the greatest increase in prevalence of obesity, accept personal responsibility? The CDC says obesity results from an energy imbalance, by eating too many calories and not getting enough physical activity. Big Food says it's a lack of activity, the TV industry says it's the diet. The Atkins people say too much carbohydrate, the Ornish people say too much fat. The juice people say it's the soda, the soda people say it's the juice. The schools say it's the parents, the parents say it's the schools. How are we going to fix this, when no one will take responsibility? If you want to just blame American apathy and laxity, all you have to

do is look at Japan and France, who have also both witnessed a doubling in the prevalence of childhood obesity in the last 10 years, as well as the rise in developing countries, in which malnutrition used to be rampant. In other words, it's not Americans; it's humans!

So far, it is just "guilt by association". The not-my-fault two-step has so far succeeded, due to a lack of mechanism, which has allowed each interest group to sidestep their responsibility. So what really has happened in the last 30 years to allow for this? And how did our physiology interact with our environment to create this problem?

HOW WE INTERPRET THE FIRST LAW OF THERMODYNAMICS

The main reason for this conundrum is our casual misinterpretation of the First Law of Thermo-dynamics, which states: "The energy within a closed system remains constant". In human terms, the First Law is usually interpreted as follows: "If you eat it (energy intake), you better burn it (energy expenditure), or you're going to store it (weight gain)". This view is buffeted by the increased caloric intake in children, while other studies document decreased energy expenditure. This interpretation of the First Law is the source of the notion that obesity is a result of the pathologic behaviors of gluttony and sloth, and allows our Government and Big Food to perpetuate the concept of "personal responsibility" for one's behavior. However, this concept of personal responsibility is not tenable in children. No child chooses to be obese. Children with childhood obesity experience a quality of life commensurate with children on cancer chemotherapy. Obese children are ostracized by their peers. Furthermore, young children are not responsible for food choices at home or at school, and it can hardly be said that preschool children, in whom obesity is rampant, are in a position to accept personal responsibility.

There is another equally plausible interpretation of the First Law, which is stated thus: "If you store it, and you expect to burn it, then you have to eat it". In this interpretation, the behaviors of gluttony and sloth become secondary to a pathological process of excess energy storage. Could this instead be what's happening? What is making energy storage go haywire?

THE HOMEOSTATIC PATHWAY: LEPTIN AND THE AUTONOMIC NERVOUS SYSTEM

To understand dysfunctional energy storage, we must first understand how our body normally regulates energy balance. Our energy intake vs. expenditure is normally regulated very tightly (within 0.15% per year) by the hormone leptin. Leptin is a 167 amino acid hormone produced by adipocytes, which transmits the primary long-term signal of energy depletion/repletion to the ventromedial hypothalamus (VMH), which controls energy balance.

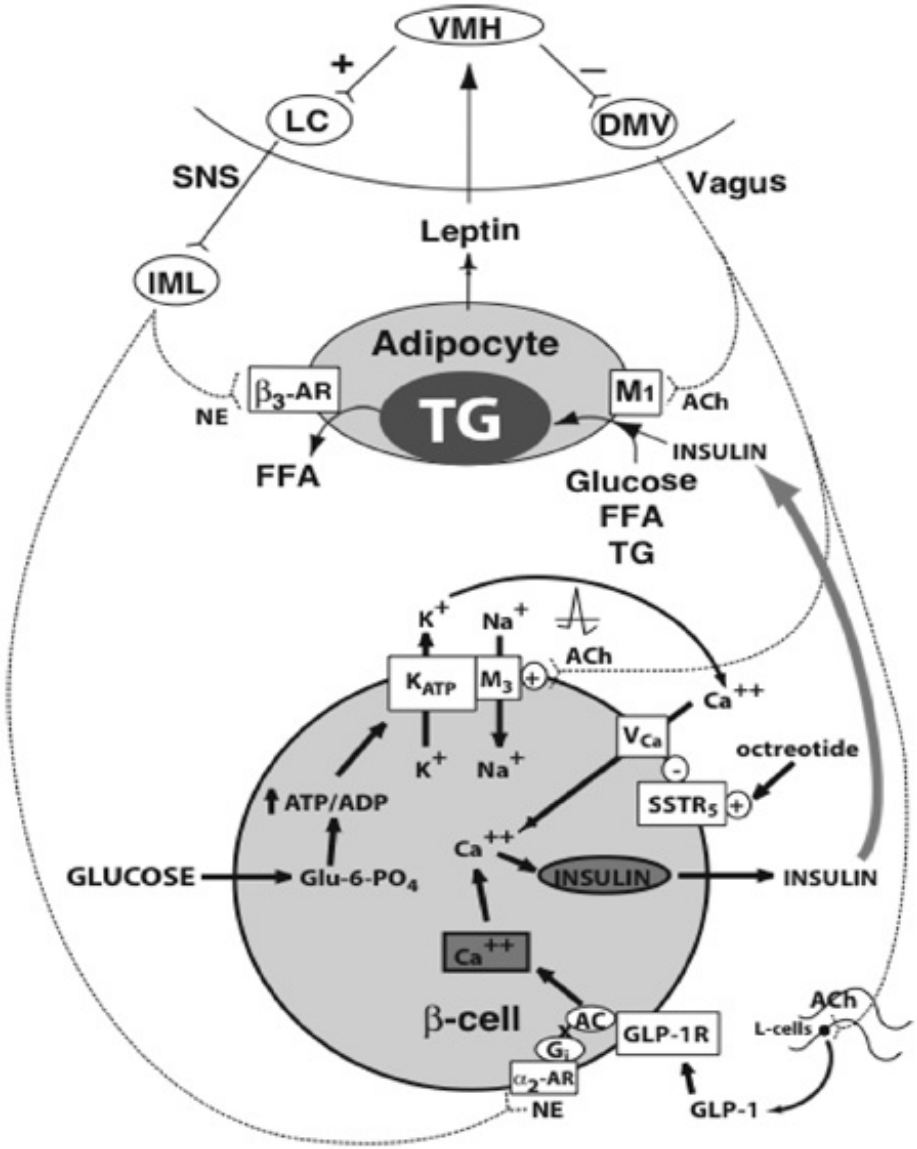

FIGURE 1. Autonomic innervation of the adipocyte and β-cell, and the starvation response. The ventromedial hypothalamus (VMH) transduces the peripheral leptin signal. Efferents from the VMH synapse in the locus coeruleus (LC), which stimulates the sympathetic nervous system (SNS). SNS pregangionic motor neurons synapse in the intermediolateral cell column (IML) of the spinal cord. From there post-ganglionic fibers emanate outward to white adipose tissue. Norepinephrine (NE) binds to the β_3-adrenergic receptor, which promotes lipolysis of stored triglyceride (TG) into free fatty acids (FFA), which are released. In addition, NE binds to α_2-adrenoceptors on the β-cell to

stimulate an inhibitory G protein, decrease adenyl cyclase (AC), and reduce insulin release. In the state of leptin deficiency (starvation), the SNS activation is quiescent, reducing lipolysis. In addition, efferents from the VMH synapse in the dorsal motor nucleus of the vagus (DMV). The vagus nerve innervates white adipose tissue. Acetylcholine (ACh) binds to the M_1 receptor, which promotes uptake of FFA and TG for lipogenesis. On the β-cell, ACh binds to a M_3 receptor, opening a sodium channel, which augments the ATP-dependent cell depolarization, increasing the calcium influx through the voltage-gated calcium channel (V_{Ca}), and increasing insulin release. Secondly, the vagus innervates L-cells of the small intestine, which secrete glucagon-like peptide-1 (GLP-1), stimulating AC, which increases free intracellular calcium, increasing insulin release. Octreotide binds to a somato-statin receptor on the β-cell, which is coupled to the V_{Ca}, limiting calcium influx and the amount of insulin released in response to glucose.

On transducing this leptin signal, the VMH does two things (**Fig. 1**). First, the VMH increases the activity of the sympathetic nervous system (SNS). The SNS increases energy expenditure by: 1) innervating the hypothalamus and appetite centers in the medulla to reduce appetite to decrease further food intake; 2) increasing TSH secretion to increase thyroid hormone release and energy expenditure; 3) innervating skeletal muscles to increase energy expenditure, by stimulating the production of ATP for muscle contractility, and also by increasing Uncoupling Proteins within mitochondria, which increase heat loss from muscle; and 4) innervating β_3-adrenergic receptors in white adipose tissue to increase lipolysis. The magnitude of energy expenditure also has a salutary effect on one's quality of life; those factors that reduce energy expenditure (e.g. hypothyroidism) reduces quality of life, while those factors that increase energy expenditure (e.g. coffee) increase quality of life (at least acutely).

Second, the VMH reduces the activity of the vagus nerve, which serves essentially the opposite role of the SNS in the regulation of energy balance, as it promotes energy storage. Inhibition of the vagus nerve: 1) speeds the heart rate, increasing myocardial oxygen consumption; 2) slows peristalsis and energy substrate absorption in the intestine; 3) reduces insulin secretion to reduce energy clearance into adipocytes; and 4) reduces adipose tissue insulin sensitivity to prevent energy accumulation in fat.

Every person has a "personal leptin threshold", above which the brain interprets a state of energy sufficiency. Thus, the leptin-replete state is characterized by increased physical activity, decreased appetite, and increased feelings of well-being.

THE STARVATION RESPONSE

Conversely, in conditions of leptin depletion, such as in the "starvation response", the VMH would of necessity decrease SNS tone (to conserve energy), with resultant decreases in feeling of well-being and decreased activity, and increase vagal tone to increase appetite and insulin release (to store more energy in adipose tissue). In the energy-replete state, humans burn energy at 50 kcal per kg fat-free mass. However, in the starvation state, this is reduced to 40-42 kcal per kg fat-free mass; in other words, starvation results in a 20% increased efficiency of energy utilization, in an attempt to conserve energy. The result of the starvation response is a rise in plasma leptin to restore the periphery, and the brain, to a state of leptin repletion.

OBESITY IS THE SAME PROCESS IN THE CNS AS STARVATION

On first thought this sounds ludicrous, but in fact, it actually makes a lot of sense. If you examine the constitutional symptoms of obese and starved individuals, they are very similar. Both are associated with fatigue, malaise, lack of activity, inability to motivate, and depression. The reason for this is the ability or inability for the VMH to transduce the leptin signal; in starvation because there is inadequacy of leptin, and in obesity because there is resistance to leptin. Furthermore, serum leptin concentrations drop precipitously during periods of short-term fasting (within 12 hours), declining faster than body fat stores, which would account for the recidivism of obesity; the hypothalamus is seeing a declining leptin signal similar to starvation, promoting increased energy intake and decreased energy expenditure. Similarly, giving leptin to obese leptin-resistant individuals is not effective.

LEPTIN RESISTANCE

So what causes leptin resistance? And what restores leptin sensitivity? So far, two paradigms for improving leptin sensitivity have been noted.

Forced weight loss

Rosenbaum et al. (JCEM 2002) employed a 10% weight loss paradigm to induce the starvation response. In these individuals, leptin declined and energy expenditure decreased. However, exogenous administration of leptin in physiologic dosing to approximate the prestarvation leptin level resulted in further weight and fat decrease, along with return of energy expenditure to the prestarvation state. In other words, in the baseline state, subjects were resistant to physiologic concentrations of leptin, while in the weight-reduced state, they were responsive to the same concentrations of exogenous leptin; thus, forced weight loss improved their leptin sensitivity.

Insulin suppression

We studied children who became obese after hypothalamic damage from brain tumors, surgery, or radiation, termed “hypothalamic obesity”. Death of these VMH neurons prevents normal leptin signaling, resulting in an “organic leptin resistance”, which manifests as a never-ending starvation response. Decreased SNS tone leads to decreased physical activity, decreased energy expenditure, and decreased quality of life. Conversely, increased vagal tone leads to increased insulin secretion, promoting incessant energy storage into adipose tissue, and intractable obesity. Hypothalamic obesity is classically unresponsive to diet, exercise, and most pharmacologic manipulations. We treated patients with the somatostatin analog and insulin suppressive agent octreotide. We were able to suppress insulin, stabilize BMI, decrease caloric intake, increase spontaneous physical activity, and improve quality of life commensurate with the degree of insulin suppression. In other words, reduction in insulin reduced hunger, fatigue, malaise, and sloth.

We then treated obese adults (without CNS lesions) with octreotide. We noted significant and progressive BMI loss in about 20% of treated subjects. Recall measurements of caloric intake demonstrated that these responders reduced carbohydrate intake selectively, along with suppression of insulin, while non-responders did not. In the responders, leptin concentration dropped by 50%, which of necessity should elicit the “starvation response”; despite this, energy expenditure increased in these subjects. We

also demonstrated that insulin suppression by octreotide correlated with improved leptin sensitivity.

WHAT CAUSES LEPTIN RESISTANCE?

Rosenbaum et al., through forced weight loss, improved leptin sensitivity as measured by improved energy expenditure in response to leptin. Insulin suppression using octreotide also improved leptin sensitivity, as measured by declining leptin with improved energy expenditure, allowing for weight loss and improved quality of life. Both paradigms share at their core a reduction in insulin concentrations. The similarity of effect between these two paradigms suggest that insulin may be a cause of leptin resistance.

Insulin antagonizes leptin signaling

Although insulin and leptin bind to separate receptors in the VMH, they share the same signaling cascade, called insulin receptor substrate 2 (IRS2)/phosphatidyl inositol-3-kinase (PI3K). It is thought that when insulin levels at the VMH are high, then leptin cannot turn on its signaling cascade. Experimental evidence in rodents suggest three separate cellular mechanisms which may account for this effect: 1) insulin excess ties up all the IRS2, and does not allow leptin to promote its signaling cascade; 2) insulin induces the protein Suppressor of Cytokine Signaling 3 (SOCS3), which dephosphorylates and inactivates the leptin receptor; and 3) insulin excess causes the buildup of the metabolite phosphatidylinositol triphosphate (PIP3), which stops the leptin-responsive neuron from firing. In any case, chronic insulin blocks leptin signaling both in rodents and in humans.

Adaptive advantage for insulin as an endogenous leptin antagonist

Teleologically, what could be the biological advantage of insulin-leptin hormonal antagonism in obesity? Leptin is a necessary signal to the VMH for the initiation of high-energy processes, such as puberty and pregnancy. If leptin signaling were not modulable, the weight accrual for reproductive competency during puberty and pregnancy would be compromised. Therefore, reversible antagonism of leptin action is in the best interest of our survival. Since insulin causes energy deposition into fat, it makes sense that it should be the central blocker of leptin as well. Indeed, both puberty and pregnancy are hyperinsulinemic and insulin resistant states, with requisite increases in insulin levels. In both, leptin levels increase acutely, and then when adulthood is reached or post-partum, insulin levels fall, weight stabilizes or is lost, and leptin returns back toward baseline. However, in maladaptive conditions when insulin rises chronically, leptin signaling is impeded, and obesity worsens.

THE HEDONIC PATHWAY: DOPAMINE AND REWARD

The homeostatic pathway is not the only central arbiter of energy balance. Complementary to insulin and leptin's ability to alter feeding behavior, these hormones also modify the "hedonic pathway" (i.e. regulation of pleasurable and motivating responses to stimuli). The hedonic pathway comprises the ventral tegmental area (VTA) and the nucleus accumbens (NA), with inputs from various components of the limbic system, including the striatum, amygdala, hypothalamus and hippocampus. This pathway

responds to drugs of abuse, such as nicotine and morphine. Food intake is responsive to activation of the hedonic pathway; for example, administration of morphine to the NA increases food intake in a dose-dependent fashion. Dopaminergic perikarya project from the VTA to the NA, which mediates the motivating, rewarding, and reinforcing properties of various stimuli, including food and addictive drugs. The VTA appears to initiate 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.

Insulin and leptin alter VTA-NA dopamine neurotransmission

Leptin and insulin receptors are expressed in the VTA, and both hormones have been implicated in modulating rewarding responses to food and other pleasurable stimuli. For instance, fasting or food restriction (where insulin and leptin levels are low) increase the addictive properties of drugs of abuse, whereas ICV leptin can reverse these effects. In rodent models of addiction, increased addictive behavior, and pleasurable response from a food reward, as measured by dopamine release and dopamine receptor signaling, is greater after food deprivation. Obesity also results in a decreased density of D_2 receptors as measured by positron emission tomography scanning.

Acutely, insulin increases expression and activity of the dopamine transporter, which clears and removes dopamine from the synapse; thus acute insulin exposure blunts the reward of food in rats. D_2-receptor antagonists and insulin act additively to acutely decrease the rewarding response to a palatable sucrose solution; furthermore, insulin appears to inhibit the ability of VTA-agonists (e.g. opioids) to increase intake of sucrose. Finally, insulin blocks the ability of rats to form a conditioned place-preference association to a palatable food.

Hyperinsulinemia may increase the reward derived from food

CNS insulin resistance may contribute to obesity by preventing insulin from extinguishing 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 the brain-specific insulin receptor knockout mice. By altering hedonic responses to food, insulin resistance at the VTA may drive excessive energy intake in a feed-forward manner.

WHERE DID THE HYPERINSULINEMIA COME FROM?

At least 3 separate reasons for hyperinsulinemia in children can be discerned. 1) *Genetics:* children from certain racial and ethnic groups have increased insulin dynamics even prior to the development of obesity, which may predispose them to increased weight gain. 2) *Epigenetics:* the “fetal origins of adult disease” hypothesis states that those born small- and large-for-gestational age at birth are prone to developing obesity; both birth weight extremes are states of hyperinsulinemia and insulin resistance, which may worsen beyond the neonatal period. 3) *Our Western environment:* through three separate submechanisms. A) Increased stress with increased cortisol secretion may lead to insulin resistance. Indeed, television watching may increase stress levels, cause increased food intake, and promote obesity. B) The loss of daily physical activity due to lack of sidewalks and

automobile transport foments insulin resistance. C) Finally, and most significantly, our current Western food environment is highly insulinogenic, as demonstrated by its increased energy density, high fat content, high glycemic index, increased fructose composition, decreased fiber, and decreased dairy content. In particular, fructose (too much) and fiber (not enough) appear to be cornerstones of the obesity epidemic, through their effects on insulin.

Fiber is good

Our Western diet is poor 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. Fiber intake may be mechanistically linked to obesity through its effects on glycemic index and energy density. 1) 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. 2) High fiber meals tend to be more satiating as they induce a greater sensation of fullness than low-fiber meals. Fiber content also tends to add bulk and viscosity to meals, thereby slowing gastric emptying. 3) Fiber-containing foods engender slower glucose absorption, which lessens the post-prandial insulin surge and decreases lipogenesis. 4) Finally, fiber leads to intestinal degradation of triglyceride to short-chain fatty acids, which inhibit insulin secretion. So why is the Western diet fiber-poor? Because you can't freeze and reheat fiber. Fast food must be shipped around the country to different franchises, thus the fiber must be removed first.

Fructose is bad

The most commonly used sweetener in the U.S. diet is the disaccharide sucrose (e.g. table sugar), which contains 50% fructose and 50% glucose. However, in North America and many other countries, non-diet soft drinks are sweetened with high-fructose corn syrup (HFCS), which contains up to 55% of the monosaccharide fructose. Thanks to its abundance, sweetness, and low price, HFCS has become the most common sweetener used in processed foods. It's not that HFCS is biologically more ominous than sucrose; it's that its low cost has made it available to everyone, especially low socioeconomic groups. HFCS is found in processed foods ranging from soft drinks and candy bars to crackers to hot dog buns to ketchup. Average daily fructose consumption has increased by over 25% over the past 30 years. The growing dependence on fructose in the Western diet may be fueling the obesity and T2DM epidemics.

Animal models demonstrate that high-fructose diets lead to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance, which suggest that fructose consumption is playing a role in the epidemics of insulin resistance and obesity and T2DM in humans. The metabolism of fructose differs significantly from glucose. Fructose is absorbed in the intestine and enters the liver without insulin regulation. There, fructose is converted to fructose-1-phosphate (F1P), consuming ATP and increasing the formation of uric acid, which suppresses the action of nitric oxide on vascular smooth muscle and promotes hypertension. F1P enters the glycolytic pathway without regulation. This leads to an accumulation of xylulose-5-phosphate, which stimulates the process of de novo lipogenesis, increasing VLDL production, which promotes atherogenesis. The glycolysis of fructose ultimately leads to an overaccumulation of acetyl-CoA in the hepatocyte, some of which cannot be

metabolized through the Krebs cycle; therefore it is then reassembled into free fatty acids (which promote pancreatic insulin hypersecretion) and triglycerides (some of which precipitate in the liver and cause hepatic insulin resistance and non-alcoholic steatohepatitis). Fructose also does not suppress secretion of the so-called “hunger hormone” ghrelin, levels of which correlate with perceived hunger. In sum, fructose consumption has metabolic and hormonal consequences different from glucose, that facilitate development of obesity and the complications of the Metabolic Syndrome. The highest fructose loads are soda (1.7 gm/oz) and juice (1.8 gm/oz).

SUMMARY

Insulin does three things which put it front and center in the obesity cascade. 1) Insulin drives energy into fat for storage. 2) Insulin interferes with leptin signaling. This results in weight gain and leptin resistance, which results in decreased SNS activity, reducing energy expenditure and physical activity; and increased vagal activity, which promotes further insulin secretion and energy storage. 3) Insulin interferes with the clearance of dopamine, thus increasing the reward of food. Thus, hyperinsulinemia turns the negative feedback system of energy balance into a “vicious cycle” of obesity. Externally, this appears as “gluttony and sloth”, but it is biochemically driven.

How does this work? A thin, insulin sensitive, 13 year old might consume a daily allotment of 2000 kcal, and burn 2000 kcal daily (or 50 kcal per kg fat-free mass) in order to remain weight-stable, with a stable leptin level. However, if that same 13 year old became hyperinsulinemic and/or insulin resistant, perhaps as many as 250 kcal of his daily allotment would be shunted to storage in adipose tissue, promoting a persistent obligate weight gain. Due to the obligate energy storage, the child now only has 1750 kcal per day to burn. The hyperinsulinemia also results in a lower level of leptin signal transduction, conveying a central signal of energy insufficiency. The remaining calories available are lower than his energy expenditure; the CNS would sense starvation. Through decreased SNS tone, he would reduce his physical activity, resulting in decreased quality of life; and through increased vagal tone, he would increase caloric intake and insulin secretion, but now at a much higher level. Furthermore, the reward of eating does not shut off, continuing the process. Thus, the vicious cycle of gluttony, sloth, and obesity is promulgated (**Fig. 2**).

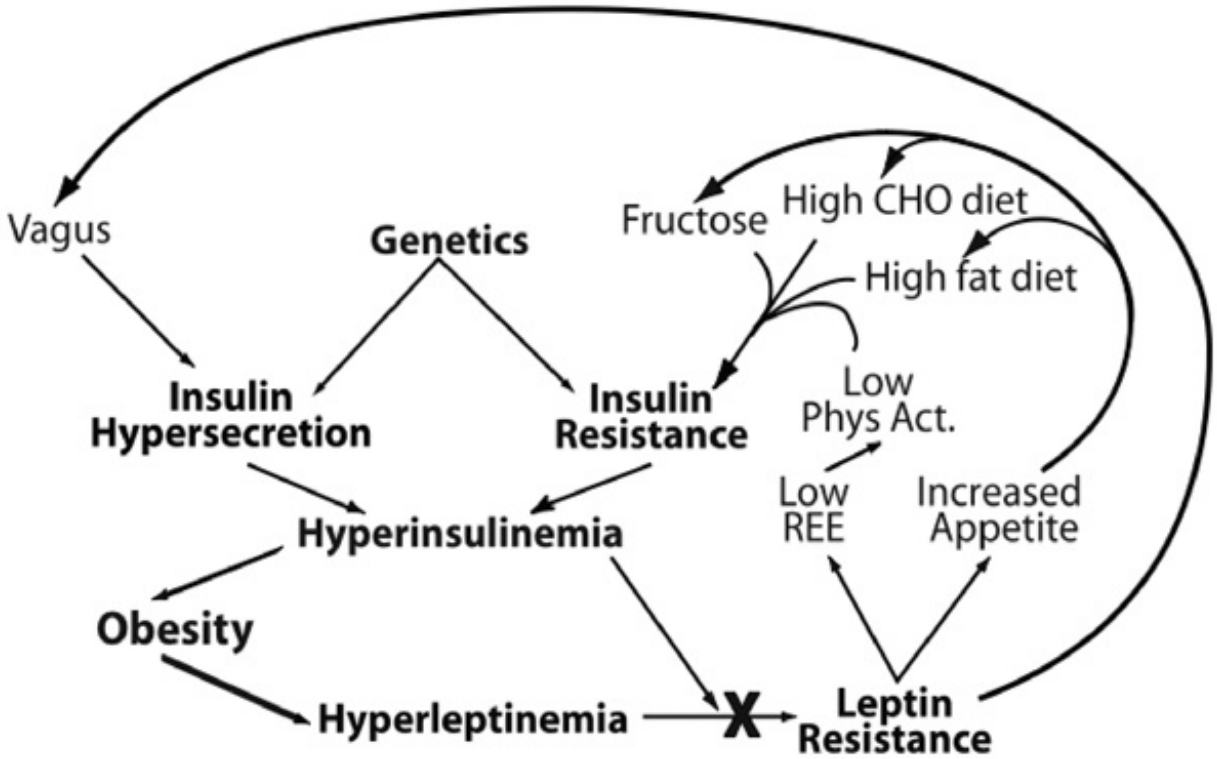

FIGURE 2. Algorithm describing the role of hyperinsulinemia in the dysfunction of the energy balance pathway, by promoting energy storage into adipocytes, and by interfering with leptin signal transduction, which turns a negative feedback pathway into a vicious cycle.

Is this personal responsibility, when a kid's brain thinks it's starving? Is it personal responsibility when a mother of a 2-month old asks her pediatrician if it's time to start juice? Is it personal responsibility when the American Academy of Pediatrics still recommends juice for toddlers? Is it personal responsibility when the first ingredient in the barbecue sauce is high-fructose corn syrup? Is it personal responsibility when in order to meet the criteria for No Child Left Behind, the school does away with P.E.? We must get the insulin down. Fixing the food supply and promoting physical activity for children can't be done by government, and won't be done by Big Food. This will require a grass roots, bottom-up effort on the part of parents and community leaders. We as physicians must lead the way.

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