Childhood Obesity: Adrift in the "Limbic Triangle"

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chronic disease, hypothalamus, insulin, cortisol, environment

Abstract

The prevalence and severity of childhood obesity have increased steadily over the past three decades. The human species evolved to rigorously defend its lower limit for weight and adiposity but is tolerant of the upper limit, which, until recent times, was rarely approached. Neuroendocrine mechanisms within the limbic core of the brain prevent starvation (ventromedial hypothalamus), heighten reward (ventral tegmental area and nucleus accumbens), and attenuate stress (amygdala), in order to promote food-seeking and ingestive behavior and to conserve energy output. In a stressful modern environment with ready access to calorie-dense, highly palatable foods and limited venues for activity, normal, reflexive responsiveness to these three drives makes weight gain all but inevitable. The obesity that ensues often engenders insulin resistance, which undermines the ability of normal hunger and satiety signals to accurately modulate energy intake versus expenditure. Obesity interventions that rely on cognitive information alone cannot free children from this "limbic triangle." Integrated multidisciplinary family- and community-based education, effective stress reduction, and a societal commitment to alter the food and built environments are all necessary components to battle the global obesity epidemic.

THE USUAL (AND NEWER) SUSPECTS

The steady increase in both the prevalence and severity of childhood obesity over the past three decades (1) has continued unabated despite the parallel increased attention science and society have devoted to this problem (2). It currently seems unlikely that the United States will reach the ambitious goal set forth in Healthy People 2010 to reduce the prevalence of obese children to 5%. This failure is not for lack of knowledge of the First Law of Thermodynamics, normally interpreted to implicate behaviors of increased caloric intake and/or decreased energy expenditure. Nor is it for lack of appreciation of the severity of either the personal health burden (3) or societal cost of this burgeoning epidemic (4).

A wealth of evidence supports a role for decreased physical activity (5), increased television time (6), and increased consumption of sugar-sweetened beverages (7) in the current rise in childhood obesity. Less compelling data attribute blame to lack of breastfeeding (8), skipping breakfast (9), reduced intake of fruits, vegetables (10), and other sources of dietary fiber (11), fewer family meals (12), and more fast food restaurant dining (13). Although legislation and health policy are attempting to tackle some of these putative root causes (14), progress is impeded by numerous individual, community, industrial, and societal barriers. A recent review made a compelling case for ten additional factors that favor persistent weight gain in the U.S. population at large: sleep debt; endocrine disruptors in the food chain; decreased variability in ambient temperature due to heating and air conditioning; decreased smoking; increased use of pharmacotherapies (notably steroids and antipsychotics that alter energy balance); demographic changes toward ethnicities with higher prevalences of obesity and toward older age brackets in which individuals are more likely to accumulate extra adiposity; increase in gravida age; greater reproductive fitness at moderate degrees of overweight [although severe overweight promotes infertility (15)]; and assortative mate selection for obesogenic genes (16). Others posit that obesity is the result of chronic stress in modern life, coupled with frequent dieting or self-imposed food restriction, with synergistic effects that increase the reward value of palatable foods (17). The increasing prevalence of micronutrient deficiencies in highly processed, energy-dense diets can be linked to numerous chronic conditions including obesity (18, 19). A link between changes in our gut microbial flora and the increasing prevalence of obesity, metabolic syndrome, and type 2 diabetes has also been postulated (20).

Although the contribution of any one of these risk factors may be small, their combined impact is probably considerable and possibly synergistic (21). Indeed, the combination of risk factors found in our modern environment seems to make weight gain the default tendency for the majority of the human species, as exemplified by the increasing prevalence of obesity worldwide (22). Health awareness and attitude improves with a public health media campaign over time, but without parallel changes in health behavior; knowledge alone is insufficient motivation (23). Even more concerning is the lack of efficacy of almost every lifestyle intervention attempted in children (24, 25). Obese children who fail lifestyle interventions are often deemed noncompliant, but it is increasingly clear that individual effort is no match for genetics coupled with a toxic environment.

This review outlines the complex network of genetic, behavioral, and environmental barriers that thwart our best attempts to restore or even maintain a healthy body weight. We propose that starvation, reward, and stress trigger three human physiologic survival mechanisms that underpin energy homeostasis and contribute to our current mismatch between health knowledge and behavior, favoring weight gain.

HOW MUCH OF OUR INGESTIVE BEHAVIOR DO WE REALLY CONTROL?

Genetics

The identification of several exceedingly rare Mendelian monogenic syndromes affecting hunger and satiety pathways in the central nervous system (CNS) (26) has deepened our understanding of genetics in the elaboration of common obesity. Mutations in genes for leptin, leptin receptor, proopiomelanocortin, prohormone convertase 1, melanocortin 4 and 3 receptors, and SIM1 all disrupt the physiologic cross-talk between peripheral signals and the hypothalamic receptors for energy balance. Melanocortin-4 receptor gene mutations are the most common, accounting for ~5% of children with morbid obesity (27). The other monogenic conditions together have been identified in fewer than two dozen individuals worldwide (28). Defects in these genes and their regulatory pathways lead to a phenotype of abnormal eating behavior and/or energy expenditure that results in positive energy balance from birth. Although these mutations are sporadic, they have changed the common perception that weight gain is purely volitional.

Epigenetics

Heritability for obesity has been suggested at ~50% by twin and other genetic studies (29), but the rapid escalation and magnitude of the obesity epidemic outpace the timeline required for genetic change. Recent covariance structure analysis of body mass index (BMI) using monozygotic, dizygotic, and virtual[1] twin pairs has found a significant nongenetic influence on BMI (30). This suggests that obesity is rarely genetic destiny; more often it is a tendency toward increased energy efficiency that can be sealed as "epigenetic fate" when the genome is situated in an obesity-promoting environment (31).

These nature-nurture epigenetic interactions that lock physiologic pathways into predictable phenotypes are thought to occur after conception but before birth. The fetal origins hypothesis states that some aspect of the uterine environment contributes to the development of obesity and diabetes in later life (32). Evidence is seen in babies born small or large for gestational age (SGA, LGA) or premature, who later develop obesity, insulin resistance, and type 2 diabetes. Prenatal programming can be replicated in animal models of caloric restriction during pregnancy leading to SGA at birth, with the development of obesity and diabetes in adulthood (33). Similarly, gestational diabetes mellitus, as well as simple maternal obesity or excessive weight gain during pregnancy, are significant risk factors for fetal hyperinsulinemia and LGA (34), which also results in obesity and the metabolic syndrome (35). Converging data support the hypothesis that individuals may also experience lifelong remodeling of their epigenomes due to nutritional exposures, normal aging, stress, or disease states during postnatal development (36). These processes include chromosomal instability, telomere shortening, mitochondrial deteriorations, and oscillatory circadian rhythmic expression of clock genes. Better understanding of genome epigenetic control may be necessary to fully elucidate the molecular mechanisms of obesity and associated disorders. This emerging field may also help explain the critical role of the environment in the development and progression of disease.

BMI: body mass index

BRAIN REGIONS THAT CONTROL REDUNDANT MECHANISMS FAVORING WEIGHT GAIN

The control centers for appetite regulatory signals and energy expenditure at the root of

[1]Virtual twins are children the same age who have been reared together from infancy but are not genetically related.

VMH: ventromedial hypothalamus

VTA: ventral tegmental area

NA: nucleus accumbens

energy mismatch lie deep within three areas of the primitive limbic system of the brain. Each of these centers perceives a separate but complementary sensation that drives ingestive behavior. Descending projections of hypothalamic neurons can in turn powerfully modulate food intake by changing the capacity of direct satiety signals at the level of the caudal brainstem.

The Ventromedial Hypothalamus and Starvation

The ventromedial hypothalamus (VMH), composed of the ventromedial nucleus and arcuate nucleus, mediates complex afferent and efferent neuroendocrine signals necessary for energy homeostasis. VMH neurons contain receptors for and receive afferent signals related to adiposity (leptin), nutrient metabolism (insulin), hunger (ghrelin), and satiety (peptide YY_{3-36}) (37). The VMH in turn transduces these afferent hormonal signals via the paraventricular nucleus and lateral hypothalamic area, through neurons containing the melanocortin-4 receptor, to either stimulate or suppress appetite and to adjust energy expenditure accordingly (38). Efferent signals are then transmitted that activate either of the two components of the autonomic nervous system; sympathetic activation promotes energy expenditure via gluconeogenesis and lipolysis, and parasympathetic activation promotes energy storage through lipogenesis. Decline in leptin signal transduction is interpreted by the VMH as starvation, which promotes sympathetic reduction to conserve energy and parasympathetic activation to store energy (39). This phenomenon is at work in animal models with VMH lesions (40) and in children with brain tumors (41) who manifest hypothalamic obesity, resulting in neurally mediated pancreatic insulin hypersecretion, sympathetic reduction, and intractable weight gain even upon food restriction (42, 43).

The Ventral Tegmental Area, Nucleus Accumbens, and Reward

Positron emission tomography suggests that these hunger and satiety neuronal circuits in the VMH connect to other regions of the limbic system (44), where primal emotions, reproductive drive, and survival instinct are housed, such that complex orexigenic and anorexigenic peptides trigger a "mindless" ingestive response. In order to maintain eating as one of the most powerful urges in animal and human behavior, evolution has also made it a rich source of pleasure and reward. It has been argued that the impasse in the efforts to both treat and prevent obesity stems from the intrinsic difficulty of overriding instinct with reason (45).

The limbic structures of the hedonic pathway that make food intake rewarding are the ventral tegmental area (VTA) and nucleus accumbens (NA). The NA is also referred to as the pleasure center of the brain; this is the area responsive to morphine, nicotine, and ethanol. Compulsive food intake is a reflexive reaction to stimulation of this reward pathway, as evidenced by morphine microinjection into the NA (46). Dopamine neurotransmission from the VTA to the NA mediates the reward properties of food (47), especially under stress (48). The palatability of available food further undermines normal satiety signals and motivates energy intake independent of energy need (49). Sweet and high-fat foods mobilize both endogenous opioids and dopamine and establish hard-wired pathways for craving in the NA and VTA that can be identified by functional magnetic resonance imaging (50). In obese subjects, dopamine D_2 receptor abundance is inversely related to BMI, fueling a perceived need for compulsive food intake to provide excess stimulation of depressed circuits. Similarly, drugs that block D_2 receptors (e.g., antipsychotics) are associated with a higher risk of obesity (51). Under normal circumstances, leptin and insulin signal adipose and nutrient sufficiency to the VTA, suppressing dopamine

neurotransmission and the reward of food (52). However, these negative feedback loops are blocked by the states of insulin and leptin resistance that characterize obesity (53).

The Amygdala and Stress

The VMH and VTA-NA mediate satiety when energy stores are replete, but appear to be easily overridden by amygdala activation and resultant stress, a state of physiologic insulin resistance (54). Numerous lines of evidence suggest that the stress glucocorticoid corticosterone (in the rat) or cortisol (in the human) is essential for the full expression of obesity (43), which helps to explain the disruptive role of stress in weight regulation (48).

Stress and glucocorticoids are integral in promoting adiposity and the metabolic syndrome. Adrenalectomized rats maintained pharmacologically with high levels of corticosterone demonstrate that exogenous fat intake is directly proportional to circulating corticosterone concentrations (55), while amygdala activation by stress is dampened by the ingestion of energy-dense food (56). In intact rats, corticosterone stimulates eating, particularly of high-fat food, and in humans, cortisol administration also increases food intake (57). Human research shows increased caloric intake of "comfort foods" (i.e., those with high energy density) after acute stress (17). Several studies in children have observed relationships between stress and unhealthy dietary practices, including increased snacking (58), and elevated risk for problems with weight during adolescence and adulthood (59). In a controlled study of 9-year-olds, children who both scored high on dietary restraint and felt more stressed by lab challenges tended to eat more comfort food (60).

ADIPOSE-GUT-BRAIN SIGNALS THAT FAVOR WEIGHT GAIN

Food ingestion is much more complex than intake of addictive drugs because it is modulated by both peripheral and central signals (51). Peripheral afferent hormonal signals that originate in the intestinal tract continually inform the CNS about the status of acute hunger versus satiety. The hunger peptide ghrelin increases food intake and body weight by stimulating VMH orexigenic neurons (61). Contrary to satiation peptides, ghrelin also decreases insulin secretion. Ghrelin levels normally rise during fasting and fall upon eating, suggesting a role in meal initiation and termination. Increasing evidence indicates that ghrelin also acts on midbrain pathways governing reward through neural circuits that process the hedonic properties of food (62). Postprandial ghrelin suppression is independent of luminal nutrient exposure in either the stomach or the duodenum, where 80%–90% of this gut peptide is produced. Instead, it results from neurally transmitted, nonvagal intestinal signals, augmented by insulin and muted by insulin resistance (63). Fasting ghrelin levels are lower in obesity and states of insulin resistance and fail to decline further with food intake, which may contribute to overeating (64). Other intestinal peptides in the afferent system include cholecystokinin (CCK), glucagon-like peptide-1 (GLP-1), and peptide $YY_{(3-36)}$ (PYY), all of which promote satiety by binding to receptors in the VMH and caudal brainstem (65). But as with ghrelin, both fasting and postprandial responses of GLP-1, PYY, and CCK levels are diminished in obese subjects compared with normal controls, potentially further contributing to dysfunctional appetite regulation (63). Furthermore, whereas in normal-weight individuals these hunger and satiety signals confer protection against obesity, differential postprandial brain signaling with gut peptides in obese versus lean individuals suggests neural underpinnings of hyperphagia that would be expected to favor weight gain (66).

Adipose tissue, especially visceral adipose, has major signaling functions in obesity. It secretes several hormones, notably leptin and adiponectin, and a growing list of adipokines involved in inflammation and the

acute phase response, processes that link obesity to its most significant comorbidities via the metabolic syndrome (66a). The recent discovery of a direct brain-adipocyte link has also connected chronic stress to obesity and the metabolic syndrome. Neuropeptide Y (NPY), a peptide derived from the brain and sympathetic nerves upon stimulation by various stressors, has potent orexigenic activity. In a glucocorticoid-dependent positive feedback loop, NPY stimulates its own production and upregulates its receptors in abdominal fat, stimulating fat angiogenesis, proliferation, and macrophage infiltration (66b). What ensues is a self-perpetuating cycle of peripheral fat generation, inflammation, and central appetite stimulation, fueled by stress-induced sympathetic activation.

INSULIN IS AN ENDOGENOUS LEPTIN ANTAGONIST

Insulin and leptin convey information to the CNS regarding long-term peripheral energy homeostasis. Both these hormones are secreted during periods of energy sufficiency, their receptors colocalize to the same VMH and VTA neurons, and both have similarly anorexigenic effects when administered acutely into the cerebrospinal fluid (37). However, obesity is a state of chronic hyperinsulinemia and hyperleptinemia in the face of insulin and leptin resistance, and the negative feedback on food intake that should result from VMH exposure to both hormones is ineffective. This system paradoxically becomes a positive feedback loop or "vicious cycle" in obesity (67). Appetite remains uncurbed and weight accrues despite excess energy stores.

Although insulin and leptin bind to separate receptors in the neurons of the VMH and VTA, they share the same signaling cascade, called insulin receptor substrate 2 (IRS2)/phosphatidyl inositol-3-kinase (PI3K) (67), and thus hyperinsulinemia may block leptin signaling. Furthermore, leptin transport across the blood-brain barrier is impaired by hypertriglyceridemia, which occurs both in starvation and with the insulin resistance of obesity (68). Because leptin communicates the level of adipose stores to the brain, leptin resistance in the VMH invokes the starvation pathway and promotes increased caloric intake. Leptin resistance in the VTA simultaneously invokes the hedonic pathway, making food a more potent reward.

Both obesity and starvation are states of free fatty acid mobilization and insulin resistance (69). In both states, the VMH transduces a deficient leptin signal—in starvation because there is inadequacy of leptin, and in obesity because there is resistance to leptin (70). Furthermore, serum leptin concentrations drop precipitously during periods of fasting (within 12 h), declining faster than body fat stores (71). This helps explain the recidivism of obesity; the hypothalamus reads a declining leptin signal as starvation and promotes increased energy intake and decreased energy expenditure.

Teleologically, what could be the biological advantage of insulin-leptin hormonal antagonism? Leptin is a necessary signal to the VMH for the initiation of high-energy processes such as puberty and pregnancy (72). If leptin signaling were not modulable, the weight accrual required for reproductive competency during puberty and pregnancy would be compromised. The reversible antagonism of peripheral leptin action by insulin is advantageous for survival; since insulin causes energy deposition into fat, it makes sense that it should also be the central blocker of leptin. Indeed, both puberty and pregnancy are insulin-resistant states with requisite increases in insulin levels. In both, leptin levels increase acutely, and afterward insulin levels fall, weight stabilizes or is lost, and leptin drops back toward baseline (73).

AN ANCIENT "LIMBIC TRIANGLE"

Redundant pathways at several levels of gene transcription and control contribute to an energy-conserving phenotype that favors

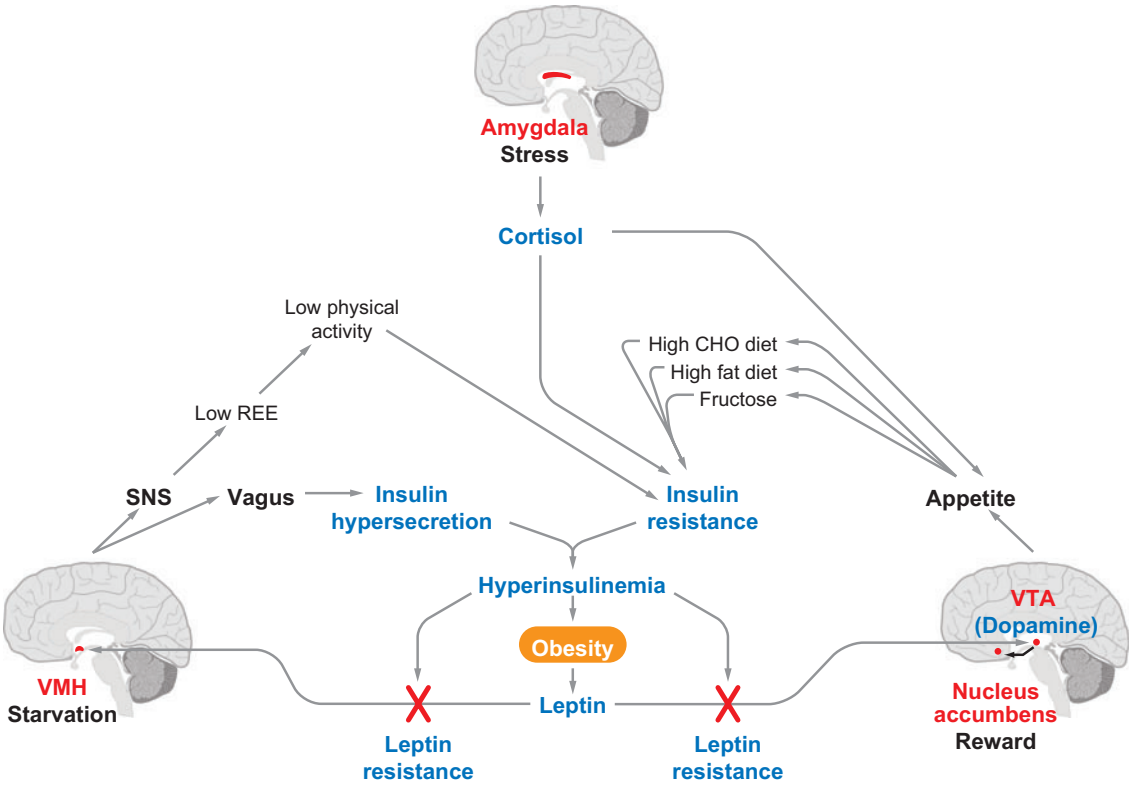

Figure 1

The "limbic triangle." Three areas of the CNS conspire to drive food intake and reduce physical activity, resulting in persistent weight gain. The ventromedial hypothalamus (VMH) transduces the leptin signal from adipocytes to reduce energy intake and increase energy expenditure; however, hyperinsulinemia prevents leptin signaling, promoting the "starvation response." The ventral tegmental area (VTA) transduces the leptin signal to reduce dopamine neurotransmission to the nucleus accumbens (NA), reducing food intake; however, hyperinsulinemia prevents leptin signaling here as well, increasing dopamine and promoting the "reward" of food. The amygdala transduces fear and stress, which results in increased cortisol release from the adrenal cortex. The elevated cortisol also drives energy-rich food intake and promotes insulin resistance, further interfering with leptin signaling at the other two CNS sites. Thus, activation of any aspect of the limbic triangle turns on a positive feedback loop, promoting continued weight gain and obesity. CHO, carbohydrate; REE, resting energy expenditure; SNS, sympathetic nervous system.

hyperinsulinemia. Each corner of the limbic triangle (**Figure 1**) is vulnerable. Chronic insulin action at the VMH inhibits leptin signaling, which is interpreted as starvation; this in turn decreases sympathetic activity (reducing energy expenditure) and increases vagal activity (promoting energy storage). Chronic insulin action at the VTA, by inhibiting leptin signaling, dysregulates hedonic reward pathways, which in turn increases food-seeking behavior, especially for high-fat and high-sugar foods, and this results in excessive energy intake. Chronic activation of the amygdala under conditions of stress, depression, or anxiety increases secretion of cortisol, which is itself an orexigen and accumulator of visceral fat, and which promotes insulin resistance to further inhibit leptin signaling and perpetuate the vicious cycle of hyperinsulinemia and accelerated weight gain. Key risk factors identified in the current obesity epidemic, namely physical inactivity, television

viewing, and high intake of sugared beverages, directly stimulate the limbic triangle by fomenting hyperinsulinemia. Television viewing, one of the most modifiable causes of childhood obesity, displaces time for physical activity (74), provides constant exposure to advertising for high-fat, sugar-laden processed foods, and the opportunity to mindlessly indulge in them (75).

On the caloric expenditure side, the benefits of physical activity are numerous, but improved insulin sensitivity is central to its ability to prevent obesity (76). Insulin sensitivity is a prerequisite for leptin sensitivity and central energy regulation. In the European Youth Study, cardiorespiratory fitness was more strongly correlated with metabolic risk than was total physical activity, but predictably, total and vigorous physical activity were inversely associated with metabolic risk (77). A systematic review of controlled physical activity interventions in children concluded that the main factor distinguishing effective from ineffective lifestyle trials (i.e., trials involving behavioral modification without drugs) was that effective ones included moderate to vigorous aerobic activity on a relatively compulsory rather than voluntary basis (78). Exercise is also a proven stress reducer, critical to the success of cardiovascular health promotion efforts (79, 80).

On the caloric intake side, insulin resistance is promoted by "junk foods" (81), arguably owing to both the abundance of fructose and lack of fiber. Average daily fructose consumption in the United States has increased by >25% over the past 30 years (82). Animal models and human data demonstrate that high-fructose diets lead to increased energy intake, decreased resting energy expenditure, excess fat deposition, and insulin resistance (83). Cohort studies of adults demonstrate that increased fiber intake is inversely associated with weight gain, insulin resistance, and risk of type 2 diabetes mellitus (84). An inverse association between fiber intake and the metabolic syndrome has also been described in children (85). Fiber-containing foods retard glucose absorption, which lessens the postprandial insulin surge and decreases lipogenesis (86). In addition, high-fiber meals allow for delivery of undigested triglyceride to the colon, favoring intestinal flora responsible for fermentation to short-chain fatty acids whose absorption generates a less atherogenic lipoprotein profile and decreases insulin secretion (87). Archeologists surmise that our ancestors used to consume 100–300 g of fiber per day; current dietary fiber intake is 12 g/day (88). High-fiber food choices are generally also lower in glycemic load, which, by lowering insulin, can improve leptin sensitivity. This suggests that physiologic adaptations to energy metabolism can be modified by dietary composition (89).

WHY OUR CURRENT STRATEGY DOESN'T WORK

The need for better approaches to childhood obesity prevention and treatment is clear, but the evidence for efficacy of most weight management strategies remains sparse and conflicted (25). We tend to seek simple, reductionist etiologic mechanisms for a chronic, multifactorial, and arguably hard-wired condition. Given the redundancy and synergism of the CNS pathways, the relative ease with which satiety signals are overridden, and the fact that leptin falls prior to insulin during caloric restriction (71), it should not be surprising that dieting alone results in almost universal recidivism. In other words, once you enter the limbic triangle, it is virtually impossible to get out unassisted.

For lifestyle modification to be effective, all three limbic areas involved in the triangle need to be addressed. This is difficult and expensive. Education concerning nutrition and exercise is necessary to help individuals negotiate our current toxic environment (45), but it is not sufficient to reverse the obesity epidemic in the absence of intensive family-based psychological counseling and effective stress reduction (90).

There is some evidence that adjunct pharmacologic therapy can augment the amount of weight lost with behavioral modification alone. However, pharmacotherapy alone (without behavioral modification) is not effective, and patients who respond to medication typically regain weight when the drug is discontinued (91). There is no evidence that drug therapy helps jumpstart a more active lifestyle and/or better nutrition, and there is little information on how safe and effective weight-loss medications are if continued for many years, especially in childhood obesity. The US Food and Drug Administration (FDA) has approved only two classes of medication for long-term use for weight loss in patients with obesity or overweight who have comorbidities: centrally acting monoamine reuptake inhibitor/appetite suppressants and intestinal lipase inhibitors (92).

Appetite suppressants attempt to interrupt the redundant pathways within the limbic brain that lead to chronic accelerated weight gain. Sibutramine, a serotonin and norepinephrine reuptake inhibitor, and one of the most commonly prescribed appetite suppressants in the United States, is approved only for patients over 16 years of age. Studied off-label as an adjunct to behavioral therapy for obese adolescents aged 12–16 years, sibutramine reduced BMI and body weight more than placebo and improved several metabolic risk factors. There were no differences in reported depressive episodes or suicide attempts between treatment groups. Maintenance of achieved weight loss beyond the one year of study and off sibutramine, however, is not known (93).

Currently, only orlistat is approved for the treatment of obesity among adolescents over age 12. A half-dose version of the drug has recently been approved for over-the-counter use. Orlistat inhibits gastrointestinal lipase and reduces by approximately one third the amount of fat that is absorbed from food. Depending on the dietary fat content, this can block intake of up to 200 kcal/day. Absorption of fat-soluble vitamins may also be compromised, an effect mitigated by concomitant multivitamin supplementation (94). The effects of orlistat are self-limited however, because meals containing >20 g fat generate intolerable side effects in the lower intestine. In conjunction with a low-fat, reduced-calorie diet, exercise, and behavioral modification, orlistat modestly improved weight management in obese adolescent participants, without any more serious side effects than mild to moderate intestinal distress (95).

Americans spend more than $1 billion each year on weight loss medications, only to learn there is no quick fix for a problem as complex as obesity. Hope springs eternal for both the growing market of obese individuals and for the pharmaceutical industry, but two inescapable issues remain: (*a*) weight-loss drugs of necessity tamper with the biochemistry of a system that is essential for survival and therefore dangerous to disrupt; and (*b*) energy balance is so important that redundancy is built into the system, making any one pharmacotherapeutic agent unlikely to be effective. Two of the more promising new classes of antiobesity agents that target central neurotransmitters and receptors involved in energy regulation have been derailed by significant adverse side effects. Rimonabant, a cannabinoid receptor inhibitor, showed promise in clinical trials in Europe but has not been approved by the FDA owing to the frequent occurrence of depression. A modified version of ciliary neurotrophic factor (CNTF) worked well in the minority of persons who did not develop antibodies, raising the intriguing possibility that neurogenesis could restore central leptin sensitivity. However, 70% of subjects tested developed an immune response that could potentially interfere with the neuroprotective effects of endogenous CNTF. The drug has not been commercialized (96).

TAKING BACK OUR HEALTH: A CHRONIC CARE MODEL

The combination of the toxic environment and the activation of the limbic triangle makes

the maintenance of normal body weight a difficult goal. In the absence of a continuous and conscious effort to maintain a healthful lifestyle, weight gain seems to be the default tendency for the majority of humans. Furthermore, due to the starvation response, the reduced-weight state is an energy-efficient one, with a 20% reduction in expended calories (97). Thus, once a person is overweight or obese, the effort required to lose weight and keep it off is considerable, as evidenced by the collective experience of individuals who belong to the National Weight Control Registry. In order to maintain an average weight loss of 30 kg for 5.5 years, they report continuous effort to restrict food intake, eat a low-fat diet and a regular breakfast, and engage in high levels of physical activity, averaging 11,000 steps per day (98). The majority (62.3%) also watch significantly less television (<10 h/week) than the reported national average of 28 h/week (99). Clearly, this minority of subjects has made the conscious decision that their health is worth exceptional and sustained effort.

American children watch an average of 3 h of television daily (100), and most eat a calorie-replete but nutritionally poor diet (101). Most overweight children also fail to meet minimum fitness standards (102). Fitness and muscular strength play a central role in whole-body metabolism. Even a relatively small difference of 10 kg in muscle mass could have a significant effect on energy balance, translating to a difference in energy expenditure of 100 kcal/day, assuming a constant rate of protein turnover (103). If a net of 100 daily kcal could be taken off the daily ledger of energy balance, this could reverse the obesity epidemic (104). Exercise helps maintain muscle tissue in children, and converting adipose tissue to muscle can help improve insulin sensitivity and health.

Because prevention of obesity in children is easier than treatment, both physicians and society must identify more compelling arguments that preventive health is worth the effort. It would help considerably if we institutionalized environmental changes that support healthy behaviors (14). The incessant din of junk food advertising, in alliance with a food-production juggernaut that pours high-fructose corn syrup, salt, and saturated and trans fats into developing brains, while seducing them into staying seated for the next show, is better funded than any health program and ruthlessly profit-oriented. However, health promotion advocates ultimately have the better product to market. A well-nourished, efficient metabolism simply generates a higher quality of life than the churning low-level inflammation associated with obesity and insulin and leptin resistance (37).

Our society has responded differently to other stimulators of the limbic triangle. The health challenges posed by tobacco, street drugs, and ethanol have been met with governmental policies of education, regulation, and interdiction. But for obesity, only education is being considered. The health care industry, health care providers, and the U.S. government must each acknowledge its unique and critical role in addressing childhood obesity and act to support implementation of health policies based on the best available evidence (105), including increased physical activity, decreased television time, and decreased consumption of sugar-sweetened beverages, including juice. Banning junk food advertising, instituting a penny tax on each teaspoon of fructose, and requiring physical activity as part of every child's afternoon either in school or in an after-school intramural program, are all ideas that have been floated but currently have enormous political opposition. The school is a natural forum in which to introduce and continually reinforce lifelong nutrition and activity skills as well as to provide the built environment in which to practice healthy eating and active living. Children at higher risk need to be identified early, and parental education must start immediately. Additional resources will be needed to support a comprehensive multidisciplinary intervention

that includes behavioral modification therapy with family participation, and both evaluation and counseling from specialists in nutrition, exercise, and medicine.

Further research into the application of a chronic care model may begin to close the gap between knowledge and behavior for obese children. Like other addictions, obesity is a chronic condition with periods of abstinence (dieting) and relapse (compulsive eating). Like other disorders of the limbic triangle, treatment will in most cases require continuous care, the use of more effective motivational counseling techniques, and links between health care providers and community programs to enhance the sustainability of clinical interventions. Group visits may be more cost-effective than one-on-one counseling and have added motivational therapeutic benefit (106). Government and financial incentives and support up front that formally acknowledge the value and necessity of lifestyle change are necessary to save both human and financial resources in the future. For childhood obesity, an ounce of prevention is worth pounds of cure.

DISCLOSURE STATEMENT

The authors are not aware of any biases that might be perceived as affecting the objectivity of this review.

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