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Minireview: Glucocorticoids—Food Intake, Abdominal Obesity, and Wealthy Nations in 2004

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Glucocorticoids have a major effect on food intake that is underappreciated, although the effects of glucocorticoids on metabolism and abdominal obesity are quite well understood. Physiologically appropriate concentrations of naturally secreted corticosteroids (cortisol in humans, corticosterone in rats) have major stimulatory effects on caloric intake and, in the presence of insulin, preference. We first address the close relationship between glucocorticoids and energy balance under both normal and abnormal conditions. Because excess caloric intake is stored in different fat depots, we also address the systemic effects of glucocorticoids on redistribution of stored energy preponderantly into intraabdominal fat depots. We provide strong evidence that glucocorticoids modify feeding and then discuss the role of insulin on the choice of ingested calories, as well as suggesting some central neural pathways that may be involved in these actions of glucocorticoids and insulin. Finally, we discuss the evolutionary utility of these actions of the stress hormones, and how dysregulatory effects of chronically elevated glucocorticoids may occur in our modern, rich societies. (*Endocrinology* 145: 2633–2638, 2004)

OUR GOAL IN this minireview is to emphasize the close relationships between glucocorticoids and stress-induced obesity and to indicate how these relationships may arise and why they are a potential source of a portion of the current epidemic of obesity in developed, rich societies. We first review the actions of glucocorticoids and the normal relationships between activity in the hypothalamo-pituitary-adrenal (HPA) axis and food intake in rodents and humans. Next, we discuss the metabolic effects of chronic elevations in glucocorticoids and the interactions between chronic stressors and these steroids, referring to our new model of chronic indirect, metabolic feedback effects of glucocorticoids. We discuss experimental results suggesting that glucocorticoids generally increase stimulus salience, including appetence, and propose that increased insulin may both inhibit normal food intake and increase the hedonic properties of high-density calories. Finally, we view our model in light of the current epidemic of obesity, with specific attention to intra-abdominal obesity, a harbinger of the metabolic syndrome, cardiovascular disease, and type II diabetes.

Close Relationship between Glucocorticoids and Energy Balance

Acute actions of elevated glucocorticoids (Fig. 1, left)

Glucocorticoids were named by Hans Selye for their major combined actions on both mobilization of small substrate molecules from peripheral fat and muscle stores and augmented gluconeogenesis in liver (1). After acute stressors, the rapid increase in HPA activity interacts with elevated epinephrine, glucagon, and sympathetic neural activity to elevate blood glucose concentrations, ensuring adequate substrate for brain and muscle that may be life-saving. The acute effects of increased glucocorticoids inhibit further activity in the HPA axis through nongenomically mediated, direct rapid-feedback actions in the hypothalamus and pituitary (2, 3). However, high cortisol (F) secretion in response to an acute laboratory stressor is also related to voluntary increases in sweet, high-fat food ingestion after the stressor (4). Individuals with high F responses to the Trier Social Stress Test chose to eat more calories comprising sweet and fat foods than did low F responders, whereas on the control day the two groups ate the same amounts. Differences in stress responses may entail rapid effects of high F (and insulin, see below) on caloric intake (4). A rapid action on caloric intake may be exerted through the effects of glucocorticoids on endocannabinoid secretion from target neurons (2).

Chronic basal actions of glucocorticoids (Fig. 1, left)

The HPA axis, CRF, and glucocorticoids are primarily concerned with energy intake, storage, and mobilization. There are very close, long-term interrelationships among feeding, metabolism, energy storage, and glucocorticoid secretion. Under *ad libitum* feeding conditions, trough corticosterone (B) concentrations [indistinguishable from those in adrenalectomized (ADX) rats] occur at the end of nocturnal feeding at lights on when insulin is high, and peak concentrations of B occur before the beginning of feeding, at lights off, when insulin is rising (5). An opposite rhythm is observed in diurnally active humans, with peak concentrations of F before the light-period activity cycle (6). Additionally, the HPA axis responds together with acute increases in insulin after meals in both rats and man (6–8). This combined

Abbreviations: ADX, Adrenalectomy or adrenalectomized; B, corticosterone; BMI, body mass index; CRF, corticotropin-releasing factor; F, cortisol; HPA, hypothalamo-pituitary-adrenal; NPY, neuropeptide Y.

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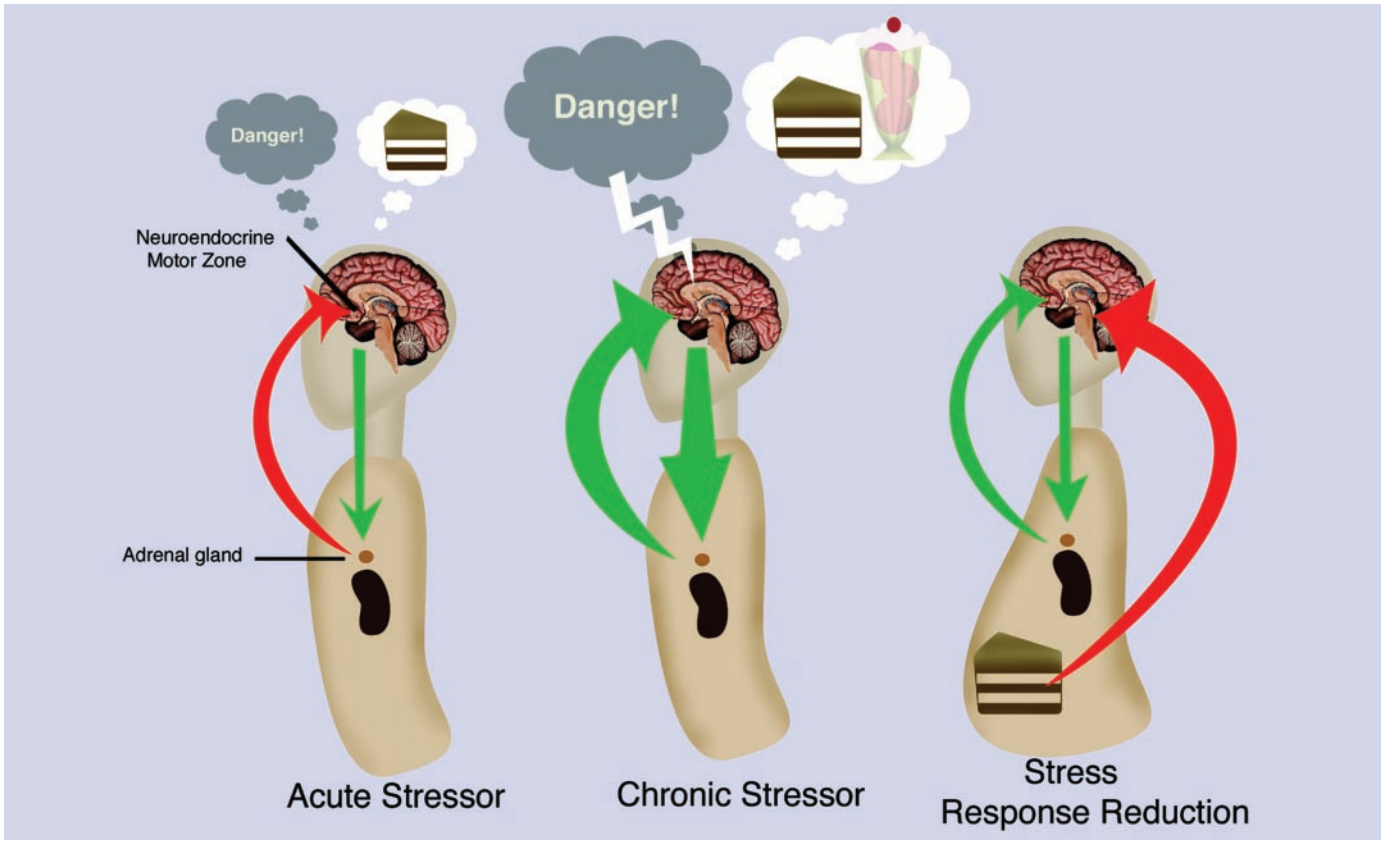

FIG. 1. Schematic of regulation of feeding and the HPA axis with acute (*left*) and chronic (*middle*) stressors, and the increased signal for stress reduction in brain that comes from increased intraabdominal fat stores (*right*). Acute stressors provoke transient increases in HPA activity that are self-limited because of rapid feedback effects of glucocorticoids on the motor output of the axis. Additionally, acute stressors alter behavior and may, through elevated glucocorticoids, enhance the motivation to eat high-sweet, fatty foods (*left*). With a chronic stressor, the elevated glucocorticoid signal acts positively on brain to promote further activation of the chronic stress response system. Glucocorticoids and insulin further augment the drive for and hedonic response to high sweet and fatty foods (*middle*). When a combination of elevated glucocorticoids and insulin has acted to increase intraabdominal caloric storage, an unidentified signal from these stores acts on brain to reduce the overall level of activity of the chronic stress response network (*right*) (47).

hormone secretion may serve to direct calorie storage into intraabdominal fat.

The circadian rhythm in glucocorticoids is both light- and food-entrainable. The food-entrainable component tracks and anticipates meal times in both rodents and humans. Restricting meals to unusual times of day phase-shifts the circadian rhythms in glucocorticoids in both rodents and people, such that it remains phase advanced relative to threshold-sized meals. In meal-fed rats, provided caloric supply is somewhat below normal, peak B levels occur just before feeding, although the light-entrainable peak remains apparent (9). People have similar F responses to shifted times of food intake (10). A group of practicing Muslims was sampled before and 23 d after the onset of Ramadan, when fasting occurs from sunrise to sunset. Daily meals were eaten at 1900 and 0100 h, and the group had shifts in F similar to those of B in meal-fed rats. Peak F concentrations occurred at lights on, but F was abnormally increased during the hours of fasting during the light, and decreased strongly after the first meal of the evening, remaining low at 0400 h, the time when F normally rises during daytime feeding (10).

Chronic increases in HPA activity resulting from stressors and malnutrition (Fig. 1, middle)

In rodents, chronic stressors usually decrease chow intake (11). In the presence of low energy stores and low insulin, daily mean glucocorticoid concentrations are invariably elevated in rodents and humans. Starvation in rats rapidly and persistently increases ACTH and B secretion, reduces negative feedback efficacy of B on HPA axis activity, and reduces insulin and leptin secretion (12). Similarly, in a model of anorexia nervosa, wherein rats are allowed restricted food with free access to running wheels, energy stores and insulin are reduced, and HPA activity is increased (13). Rats made insulin-deficient with streptozotocin both exhibit elevated glucocorticoids and eat more chow (14, 15), although much of the increased energy ingested is lost as glucose in the urine and weight is lost. Rats in the above categories exhibit the behavioral, autonomic, endocrine, and neuroendocrine characteristics of chronic stress in rodents (16). People with low fat stores and insulin concentrations such as elite athletes, fasting subjects, or those with anorexia nervosa also exhibit chronically elevated glucocorticoid concentrations (17–21). Even slight increases in F above normal with fasting are

functionally important (22). HPA activity tracks feeding, metabolism, and energy disposition under normal conditions.

Systemic Effects of Glucocorticoids on Stored Energy

Chronic hypersecretion of glucocorticoids (Fig. 1, right)

The textbook signs and symptoms of florid Cushing's syndrome include truncal obesity, relatively thin extremities, a "moon-face," and a "buffalo hump." There is a high probability of finding hypertension, increased risk of infection, and metabolic syndrome or frank type II diabetes in such individuals. Depending on the level of food intake, people with Cushing's syndrome or tonically elevated glucocorticoids of endogenous or exogenous origin may have elevated, normal, or decreased body mass index (BMI). In all of these conditions, there is a high likelihood of an elevated ratio of intraabdominal to sc fat mass (23–25), because of the glucocorticoid-mediated redistribution of stored calories into abdominal fat.

Individuals who are depressed with a high BMI appear to temper their natural depression-induced reduction in food intake (26). The inverse relationships between BMI and reduced appetite ($P < 0.0001$) and pessimistic thoughts ($P < 0.003$) in 1694 individuals with depression were defined by the Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria taken from the Montgomery-Asberg depression rating (MADRS) subscales and were corrected for gender and age. The smaller decrease in food intake in depressed individuals with high BMI may be a consequence of higher circulating insulin concentrations that accompany an increased BMI.

The specific increase in intraabdominal fat stores is a consequence of elevated glucocorticoids together with insulin. However, there need not be increased glucocorticoids in the general circulation, because elevated glucocorticoids can be generated locally in omental fat through conversion of cortisone to F via the action of 11-β-hydroxysteroid dehydrogenase type-1 (27). The active steroid is secreted directly to the liver via the portal vein (27). *In vitro*, insulin synthesis and secretion from the pancreas are directly (28) inhibited by the actions of glucocorticoids. However, *in vivo*, increasing glucocorticoids are associated with increasing insulin secretion (29), possibly because of a marked antiinsulin effect on liver (30), which appears to be particularly vulnerable to the negative effects of glucocorticoids on insulin action (31). Hepatic insulin resistance is strongly associated with abdominal obesity (32). The relatively selective increase of abdominal fat in the presence of elevated glucocorticoids and insulin may be a consequence of the differentiating effects of these hormones on stromal fat precursor cells (33), as well as increased abundance of glucocorticoid receptors on omental compared with sc adipocytes (*e.g.* Ref. 34). In cases of very low energy stores and high glucocorticoids, the normal inhibitory effects of glucocorticoids on HPA axis activity are reduced, if not abolished (11), which should enhance glucocorticoid elevations and their effects on omental fat. Thus, chronic elevations in glucocorticoids together with some insulin redistribute energy from the periphery to the center.

Modification of Feeding by Glucocorticoids and Possible Role of Insulin

Adrenalectomy (ADX), the effect of B and of palatable, high-energy calories

The key requirement for glucocorticoids for normal food intake, metabolism, and obesity is perhaps best appreciated when the effects of ADX with or without glucocorticoid replacement are studied in normal and genetically obese rodents. In normal male rodents, ADX reduces daily food intake (by 10–20%), fat stores, and the rate of ponderal weight gain (11, 35, 36) in a glucocorticoid-reversible manner (37). ADX without glucocorticoid replacement blocks both genetic-induced and neuropeptide Y (NPY)-induced obesities (38–41). In addition, many of the genetic rodent obesities are accompanied by chronically elevated glucocorticoid concentrations (42). B treatment restores genetic obesity. B also increases NPY expression, food intake, and fat preference and restores metabolism.

Thus, there is a tight correlation between metabolic status and activity in the HPA axis both acutely and chronically. Glucocorticoids are key for responding to reduced energy stores and are required for the expression of genetic obesity; under chronic conditions of low energy storage, they no longer serve to inhibit the HPA axis.

When ADX rodents are provided with high-energy fat or sucrose diets, caloric intake increases (43–46). Perhaps more surprisingly, with normal caloric intake, none of the effects of ADX that we and others have measured occur, including decreased fat depot weight, increased sympathetic neural outflow, and altered corticotropin-releasing factor (CRF) expression in the central nucleus of the amygdala and paraventricular hypothalamus (43). These results suggest strongly that without low metabolic stores and reduced insulin, ADX and chronic loss of glucocorticoids exert few effects on metabolism or on CRF expression in brain.

A new model of chronic glucocorticoid feedback (Fig. 1, right)

In light of the above, we suggested that there was a difference in kind between the acute (canonical) feedback actions of glucocorticoids and their chronic feedback actions (47). Whereas acute effects of increased glucocorticoids directly inhibit CRF and ACTH secretion, chronic effects appear to be indirectly mediated by an unidentified signal from abdominal fat stores. When B is infused directly into the brain of ADX rats, neither food intake nor body weight is corrected as they are when B is given systemically (48, 49). Possibly, the direct effects of B on CRF in amygdala activate a central stress-response network (50). The central stress-response network is recruited by chronic stressors (51) and serves to modulate behavioral, autonomic, and neuroendocrine output under conditions of chronic stress (11, 50). In the absence of chronic stress, *i.e.* with exogenous glucocorticoid treatment or Cushing's syndrome, evidence for abdominal obesity is obvious. However, if glucocorticoids are activated by chronic stressors, abdominal obesity in rats is not obvious, because chronic stress inhibits food intake, probably through the anorexigenic effects of CRF (52). Abdominal obesity in

stressed rats becomes significant when compared with nonstressed, pair-fed controls (53).

Glucocorticoid and insulin effects on caloric intake and caloric preferences (Fig. 2)

In ADX rats treated with a range of B doses, insulin is stimulated as a function of circulating B and rats eat somewhat more chow, but the feeding plateaus abruptly when B levels achieve mean daily control values. By contrast, in ADX-diabetic rats, chow intake increases in proportion to circulating B over a wide range (29). We have recently reinvestigated this phenomenon (54), studying ADX B-treated rats with and without diabetes induced by streptozotocin; however, in these experiments we allowed the rats the choice of eating chow or lard *ad libitum*. When caloric intake over a 48-h period was measured in these groups, there were B-related increases in caloric intake in both sets of rats, *i.e.* those with and those without diabetes.

B increased chow intake only slightly in the ADX rats but markedly in the ADX-diabetic rats (Fig. 2, *left*). However, lard intake was increased in a B dose-related fashion in ADX rats (Fig. 2, *middle*); by contrast, ADX-diabetic rats treated with B increased chow intake in a B dose-related fashion, and lard ingestion inhibited overall caloric intake during the first 48 h (Fig. 2, *right*). After the first 2 d, the diabetic rats shunned lard entirely and returned to B-dependent hyperphagia of chow (data not shown). There may be a parallel example to this in people. Patients with Cushing's disease and overweight-matched and normal-weight controls were tested for the pleasantness and creaminess of samples of dairy products ranging in fat content from 0–36%, and perceptions of these were similar in the three groups. When allowed to choose which they would drink, more than 50% of the subjects with Cushing's disease (with high glucocorticoids and insulin) chose products with at least 10% fat, whereas in the other two groups the high-fat products were chosen by only 20 or 30%, respectively (55).

The results of these experiments suggest (among other possibilities) that B or F increases drive for calories but that insulin may exert two actions, both probably in brain. The first, well-known effect of insulin is to inhibit orexigenic NPY synthesis and secretion in the arcuate nuclei of the hypothalamus (42). In a second effect, insulin at low concentrations could increase the palatability, or hedonic effects, of lard through its actions on catecholaminergic systems that regulate activity of cells in the nucleus accumbens (see Ref.

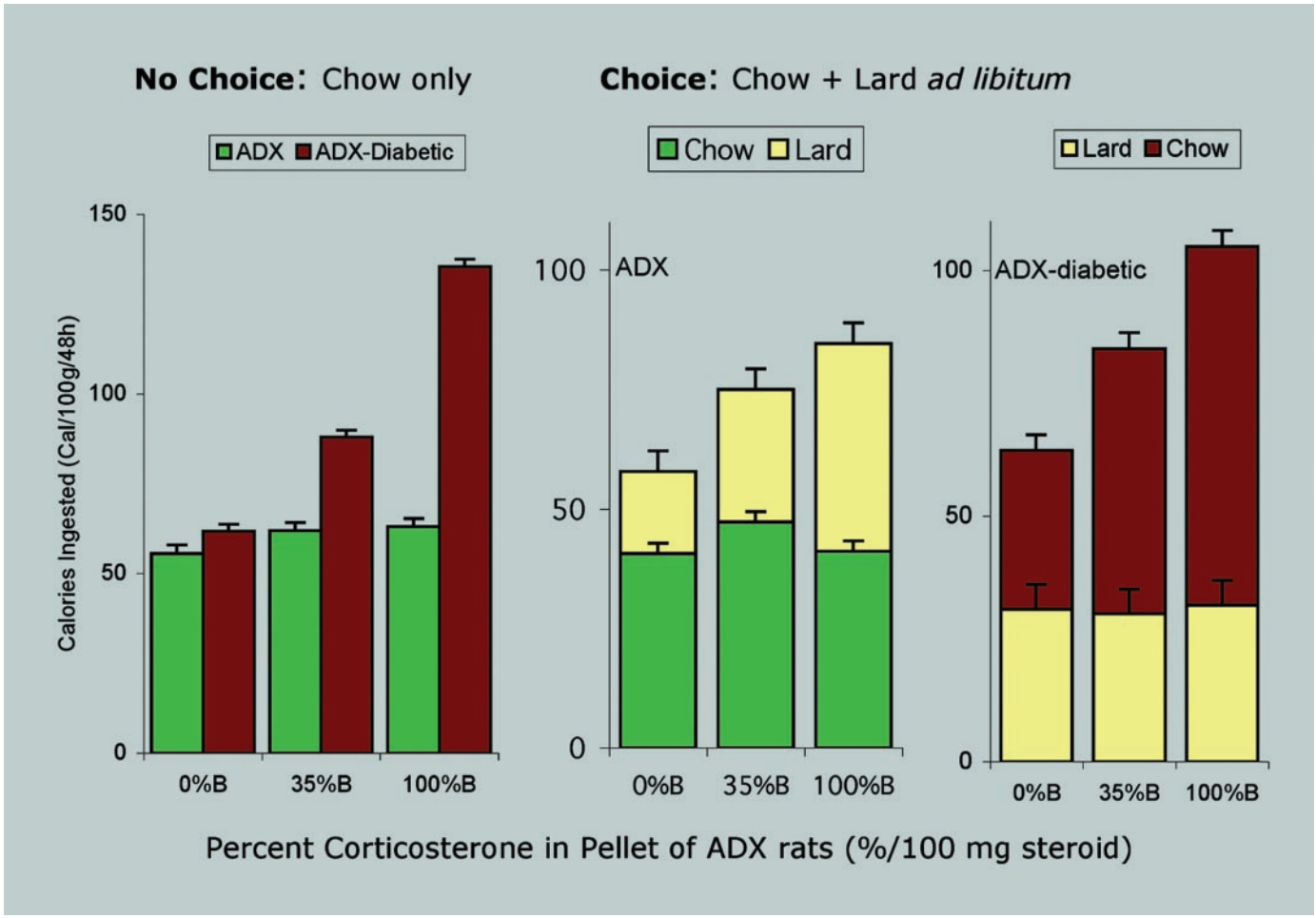

FIG. 2. Increasing B increases caloric intake as chow in the absence of insulin and as lard in the presence of insulin. During the first 48 h after offering lard, ADX-nondiabetic rats ate lard in proportion to circulating B, but ADX-diabetic rats increased chow not lard intake in response to increasing B. [Data from la Fleur *et al.: Endocrinology*, 145:2174–2185, 2004 (54). © The Endocrine Society.]

56), a brain site for reward. If this speculation is correct, then the action of insulin on activity in nucleus accumbens must be biphasically related to the insulin dose, with low concentrations stimulating and high concentrations inhibiting the palatability of high-density calories like lard. Such a biphasic dose-response curve might result from the action of low concentrations of insulin on high-affinity IGF-I receptors and higher concentrations acting on lower affinity insulin receptors (57). Insulin infused systemically to increase circulating insulin concentrations from approximately zero to normal in ADX-B-treated diabetic rats stimulates lard intake (54), however insulin infused into brains of rats with normal circulating insulin inhibits intake of both sucrose and fat (56).

The action of B seems primarily to increase motivation or drive to do something. In the absence of insulin, B increases caloric intake from chow; in the presence of insulin, B increases caloric intake from lard (Fig. 2); and in both conditions, the steroid increases total caloric intake. Similar actions of B are observed in the use of running wheels [intact rats like to run, ADX rats don't run, but B replacement restores running in a dose-related fashion (58)] and schedule-induced polydipsia (59). Similarly, responses to street drugs such as cocaine are negligible in ADX rats but increase with increasing B replacement (60, 61). Thus, glucocorticoids seem to induce increased incentive salience (62) for behaviors that can serve the organism either positively or negatively. By contrast, insulin appears to sculpt the choice of, at least, feeding behavior.

Glucocorticoid Action during Evolution and in Wealthy Societies: the Yin and the Yang

Throughout time, organisms capable of secreting glucocorticoids have had the motivation to eat, as well as the capacity to store, any excess calories and mobilize them as a consequence of the actions of glucocorticoids (*e.g.* Refs. 63 and 64). During persistent stressors, such as drought and famine, the central role of chronically elevated glucocorticoids on motivation serves organisms well. The motivational effects of the glucocorticoids drive organisms to run away or engage in search behaviors; to eat more, particularly nutritious foods; and would, at the same time, act peripherally (with insulin) to increase the immediate source of substrate for liver, the abdominal fat depots. In the absence of available food, search behaviors would still occur, but insulin would be very low, and substrate would be mobilized from available peripheral fat and protein stores. In this context also, the glucocorticoids are very important and potentially life-saving. These actions of glucocorticoids were probably selected for.

However, in wealthy societies (65), glucocorticoid actions can be a curse. It is, of course, the same effects of glucocorticoids that are mediated in societies with plenty as in those without. However, foods, particularly of high fat and carbohydrate content, are readily available, accessible, and inexpensive in our societies. Soft-drink machines selling high sucrose drinks, fast food franchises, and the propensity to eat on the run all combine to increase consumption of high-fat, high simple carbohydrate foods. Moreover, in many of these societies, there is also a high level of perceived stress. Under these conditions, glucocorticoids are engaged to store abdominal fat, resulting in high insulin and pathogenic obesity (66). Rich societies are awash in obesity; it is epidemic (67). There is a great deal of public health and pharmaceutical company effort and money oriented toward reducing obesity, through elucidating and then intervening in actions of hormones, transactivating factors, neuropeptide and fat absorption, and synthesis. Based on the physiology of the glucocorticoids and insulin, the current epidemic of obesity is, at least in large part, readily understood as a naturally occurring consequence of the ready availability of fatty and sweet foods. These two hormones promote both the ingestion of such foods and the storage of the resulting calories as abdominal fat. Changing the climate of food commerce (68) and the composition of fast foods, as well as decreasing fast food availability, could go a long way toward reducing the obesity epidemic.

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