

Chronic stress and obesity: A new view of "comfort food"

Mary F. Dallman*, Norman Pecoraro, Susan F. Akana, Susanne E. la Fleur, Francisca Gomez, Hani Houshyar, M. E. Bell, Seema Bhatnagar, Kevin D. Laugero, and Sotara Manalo

Department of Physiology and Neuroscience Program, University of California, San Francisco, CA 94143-0444

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The effects of adrenal corticosteroids on subsequent adrenocorticotropic secretion are complex. Acutely (within hours), glucocorticoids (GCs) directly inhibit further activity in the hypothalamo-pituitary-adrenal axis, but the chronic actions (across days) of these steroids on brain are directly excitatory. Chronically high concentrations of GCs act in three ways that are functionally congruent. (i) GCs increase the expression of corticotropin-releasing factor (CRF) mRNA in the central nucleus of the amygdala, a critical node in the emotional brain. CRF enables recruitment of a chronic stress-response network. (ii) GCs increase the salience of pleasurable or compulsive activities (ingesting sucrose, fat, and drugs, or wheel-running). This motivates ingestion of "comfort food." (iii) GCs act systemically to increase abdominal fat depots. This allows an increased signal of abdominal energy stores to inhibit catecholamines in the brainstem and CRF expression in hypothalamic neurons regulating adrenocorticotropic. Chronic stress, together with high GC concentrations, usually decreases body weight gain in rats; by contrast, in stressed or depressed humans chronic stress induces either increased comfort food intake and body weight gain or decreased intake and body weight loss. Comfort food ingestion that produces abdominal obesity, decreases CRF mRNA in the hypothalamus of rats. Depressed people who overeat have decreased cerebrospinal CRF, catecholamine concentrations, and hypothalamo-pituitary-adrenal activity. We propose that people eat comfort food in an attempt to reduce the activity in the chronic stress-response network with its attendant anxiety. These mechanisms, determined in rats, may explain some of the epidemic of obesity occurring in our society.

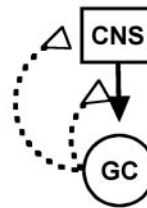
corticotropin-releasing factor | glucocorticoids | high fat | sucrose | motivation

Our understanding of regulation of function in the hypothalamo-pituitary-adrenal (HPA) axis has changed profoundly in the last decades. The discovery of functions of the distributed cell groups of corticotropin-releasing factor (CRF) neurons, the motor neurons for activation of the pituitary and adrenal, as well as the tight interrelationships between calories, body weight, energy stores, and the HPA axis have occasioned revisions in our thinking. The upshot is a new working model, the output of which is modifiable through manipulation of caloric input (Fig. 1). The long-term consequences of such output modification in chronically stressed individuals may include deleterious weight gain, abdominal obesity, type II diabetes, increased cardiovascular morbidity, and mortality. We arrived at this model through interpretation of the results from studies on manipulation of energy balance, central CRF, and the effects of acute and chronic stress and glucocorticoid (GC) treatment in intact and adrenalectomized rats.

GC Effects on HPA Function: Acute and Chronic

Canonical GC-feedback inhibition of subsequent adrenocorticotropic (ACTH) secretion is easily demonstrated acutely, within the first 18 h after stress. Acute feedback inhibition occurs in brain and pituitary (Fig. 1 *Left*), probably through nongenomic mechanisms (1). However, under a persistent stressor, or long

Canonical Model: Acute GC Feedback



New Model: Chronic GC Feedback

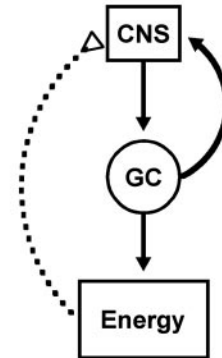


Fig. 1. Models representing the acute and chronic effects of GC on function in the HPA axis. The canonical effects occur rapidly, within minutes to a few hours after stress; GCs act directly on brain and pituitary probably through nongenomic mechanisms. The new model requires ≈ 24 h, after elevation of GC into stress concentrations. Then, the direct action of GCs on brain is stimulatory, and the negative feedback inhibition of function in the HPA axis is a consequence of metabolic effects of GC increasing abdominal energy stores.

after administration of a single stressor of high intensity (2), there is marked diminution of the efficacy of glucocorticoid feedback inhibition of stimulated, but not basal, ACTH secretion (Fig. 2 and refs. 3 and 4). After the first 24-h period of the onset of a chronic stressor, the direct long-term effects of GCs on brain are to enable the "chronic stress-response network" and thus modify a variety of mechanisms associated with coping, including enhancing stimulus salience and its attendant compulsions. It is the indirect effects of chronically elevated GCs (acting through signals of abdominal calorie storage) that inhibit the expression of the chronic stress-response network (Fig. 1 *Right*). Thus, there are three modes of GC action that are important during stress: canonical, chronic direct, and chronic indirect. We find that this new working model explains results in humans who are chronically stressed, depressed, drug-addicted, or have eating disorders.

Chronic Stress Recruits Activity in the Chronic Stress-Response Network

The minimal (e.g., see ref. 5) components of the chronic stress-response network (Fig. 3) are based on comparison of the numbers of c-Fos immunoreactive cell numbers in naive or

Abbreviations: ACTH, adrenocorticotropic; B, corticosterone; CRF, corticotropin-releasing factor; GC, glucocorticoid; HPA, hypothalamo-pituitary-adrenal; LC, locus coeruleus; PVN, paraventricular nuclei; mpPVN, medial parvicellular PVN; WAT, white adipose tissue.

*To whom correspondence should be addressed. E-mail: dallman@itsa.ucsf.edu.

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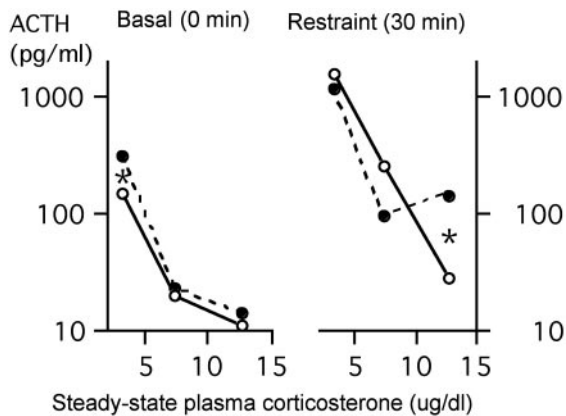


Fig. 2. In rats exposed to a chronic stressor, high GC concentrations are required to stimulate ACTH responses to novel stimuli. Adrenalectomized rats were treated with B pellets and were maintained at room temperature (solid line, open symbol) or in cold for the next 5 days (dashed line, filled symbol). Blood was sampled in the morning within 1 min (*Left*) or 30 min after the onset of restraint (*Right*; ref. 3).

chronically stressed rats that are exposed to a novel stressor shown in Fig. 2. The model also consists of a memory function that either resides in or must pass through the paraventricular nuclei (PVN) of the thalamus (6–9), because lesions or manipulation of this structure affect ACTH responses only in chronically stressed rats. The recruitment of the network could be effected by the actions of neurons in the paraventricular thalamus secreting thyrotropin-releasing hormone, which is known to strengthen synaptic connections (10, 11). Basomedial, basolateral, and central nuclei of the amygdala also have increased c-Fos cell numbers in acutely restrained rats with a chronic cold stress background, compared to acutely restrained naive rats. The amygdala appears to be a very important component of the chronic stress-response network, both because of its far-reaching innervation of cortical, subcortical, and brainstem structures, and its important role in memory consolidation (12).

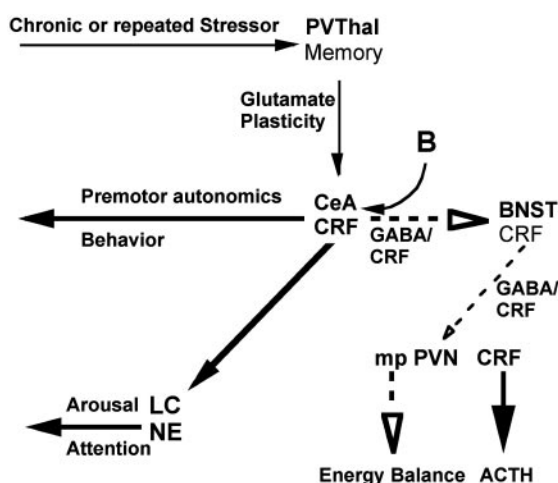


Fig. 3. Minimal working model of the chronic stress-response network. This model is based on structures that exhibited increased numbers of c-Fos-labeled cells in response to acute, novel restraint in rats with previous cold exposures compared to naive rats (6). PVThal, paraventricular nuclei of the thalamus; CeA, central nuclei of the amygdala; BNST, bed nuclei of the stria terminalis; NE, norepinephrine. Solid lines and arrows are stimulatory; dashed lines and open arrows are inhibitory.

From the stressor-activated amygdalar neurons, it is possible to elaborate behavioral, autonomic, and neuroendocrine motor outputs characteristic of chronic stress by administering CRF (13–15). Moreover, corticosterone (B) implants over the central nuclei of the amygdala increase CRF mRNA expression and anxiety-like behavior (16) and augment CRF mRNA in the hypothalamic PVN, facilitating ACTH and B responses to an acute stressor (17). Without the tonic increase in circulating B, the HPA component of the chronic stress-response network is not engaged (Fig. 2; and ref. 18). Corticosteroid-induced increases in amygdalar CRF are essential to the function of the network. Part of the increase in medial parvocellular PVN (mpPVN) CRF probably involves inhibitory inputs (GABA/CRF) to the bed nuclei of the stria terminalis (19) that appear to inhibit CRF activity in the bed nuclei of the stria terminalis (20). Activation of a double inhibitory input to the CRF neurons in mpPVN could activate (disinhibit) behavioral, autonomic, and neuroendocrine neurons. c-Fos cell numbers were increased in PVN in chronically stressed rats exposed to novel stress, compared to naive controls (6). Other limbic pathways to mpPVN could also augment CRF secretion in rats exposed to a chronic stressor (21).

CRF cells in the amygdala also innervate monoaminergic neurons in brainstem. In the locus coeruleus (LC), CRF increases the basal firing rates of LC neurons and norepinephrine secretion in the forebrain (22), probably increasing arousal and attention. Moreover, the electrical response of LC to hypotension requires amygdalar CRF input, and chronically stressed rats have increased CRF tone in the LC (23, 24). Activity of serotonergic neurons in the dorsal raphe is similarly affected by CRF and stress (25–27). Both LC and dorsal raphe had greater c-Fos responses in chronically stressed rats than in naive rats provided with a novel acute-restraint stress (6). Although systemic GCs inhibit activation of LC in adrenalectomized rats, this may be because of their peripheral corrective actions and not any direct effects on LC neurons.

Systemic Effects of GCs

As corticosteroids increase, there are strong inverse relationships between steady-state concentrations and body weight and caloric efficiency (Fig. 4 *Top*). As is well known from study of patients with Cushing's syndrome, GC concentrations in the stress range mobilize peripheral amino acids from muscle and fatty acids and glycerol from peripheral fat stores to provide fuel for glucose synthesis by liver (28). In rats, high levels of GCs inhibit growth hormone secretion, reducing linear growth, and sympathetic neural outflow, reducing some types of fat mobilization (29–31). Fig. 4 shows results from adrenalectomized rats replaced with clamped B concentrations for 5 days and allowed to drink sucrose ad libitum (32). There is a significant positive relationship between B and sucrose ingestion and B and mesenteric fat (Fig. 4 *Left Middle* and *Left Bottom*). By contrast, neither chow intake nor s.c. white fat depot weights were affected by B (Fig. 4 *Right Middle* and *Right Bottom*). Thus, passively increasing B concentrations into the stress range in rats redistributes stored energy toward an intraabdominal distribution (33). The insulin resistance that occurs with high B is probably a consequence of hepatic, rather than peripheral, tissue responses to the GCs. However, the stimulation of insulin secretion by B is essential for the redistribution of energy stores. In the absence of insulin, redistribution does not occur (30). Chronic stress usually decreases chow intake in male rats, and without pair-fed controls, central obesity is difficult to demonstrate (34). When pair-fed controls are used, stressed rats with high endogenous GCs have larger mesenteric fat depots (35). Thus, in the absence of a concurrent stressor, the GCs produce central obesity with some peripheral wasting. At the same time, clamped plasma B concentrations of 12–15 $\mu\text{g/dl}$ induce CRF mRNA in

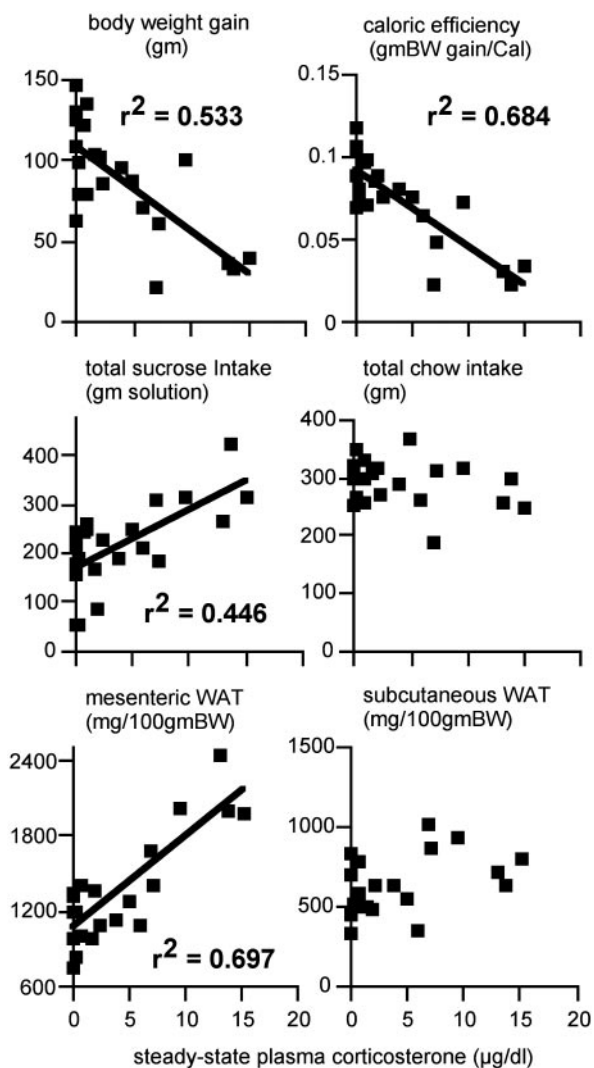


Fig. 4. B redistributes energy stores into intraabdominal sites and increases sucrose appetite. Adrenalectomized rats were replaced with a variety of doses of B and allowed to drink sucrose for a total of 9 days in a 15-day experiment (32). Significant linear regressions between B and the variable plotted are indicated by lines and r^2 values. Although high B concentrations strongly reduce both body weight gain and caloric efficiency, they increase both sucrose ingestion and mesenteric white adipose tissue (WAT) stores and have no effect on chow intake and s.c. WAT stores.

amygdala and inhibit it in the mpPVN (36, 37). Interestingly, rats with these concentrations of B are unresponsive to stressors, unless they have been previously stressed, which may relate to memorial functions of the paraventricular nuclei of the thalamus (Fig. 2 and ref. 3). Likewise, Cushing's syndrome patients who report no feelings of stress also show decreased stress responsiveness.

Sucrose Ingestion and Central B in Adrenalectomized Rats

After adrenalectomy and removal of GCs, food intake decreases, as does the rate of body weight gain (e.g., Fig. 4; refs. 31 and 38). However, when adrenalectomized rats are given concentrated sucrose (30% solution) to drink in addition to saline, the animals drink $\approx 40\%$ as much sucrose as sham-adrenalectomized controls (32), probably as a result of decreased incentive. Surprisingly, the adrenalectomized rats drinking sucrose restored weight gain, food intake, fat depots, and brown adipose tissue depot weights to normal. Uncoupling protein concentrations in

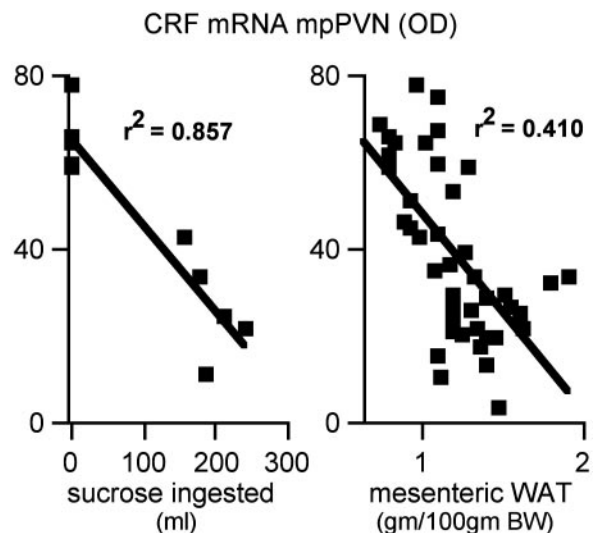


Fig. 5. Both the amount of ingested sucrose and mesenteric WAT are significantly, negatively correlated with CRF mRNA in the PVN. All points are from adrenalectomized rats without B that were given either sucrose or saccharin. The sucrose data are from refs. 32 and 38, and the mesenteric WAT results are from refs. 39 and 40.

brown adipose tissue, a measure of sympathetic outflow, were also reduced to normal, compared with sham-adrenalectomized rats drinking water (32). The analyses of HPA-relevant circuits of these rats showed that sucrose drinking reversed the depression of CRF mRNA content in amygdala and inhibited CRF mRNA in the mpPVN. In fact, there was a robust inverse relationship between the amount of sucrose consumed on the last day of the 5-day experiment and CRF mRNA in the mpPVN (39). Furthermore, drinking sucrose also inhibited elevations of dopamine- β -hydroxylase mRNA in catecholaminergic neurons of A2/C2 in the nucleus of the tractus solitarius and in the LC (39). These results suggested emphatically that if energy balance were corrected by voluntary ingestion of pleasurable calories, metabolic and neuroendocrine derangements resulting from the absence of B disappeared. This interpretation is strengthened by the fact that adrenalectomized rats drank very little equally pleasurable saccharin and exhibited the decrease in amygdalar CRF and elevation in hypothalamic CRF that are observed after adrenalectomy (32, 39).

B might act similarly to sucrose in an intersecting, or parallel, circuit in brain. To test this, we infused B into brain (100 ng/day for 6 days) in adrenalectomized rats that were allowed sucrose and/or saline to drink (40). Under basal conditions, the central steroid infusion stimulated CRF peptide in the PVN and secretion of ACTH, overriding the inhibitory effects of sucrose (40). Moreover, when sucrose-drinking adrenalectomized rats were infused intracerebroventricularly with B and repeatedly restrained, facilitated ACTH responses occurred on the third day of restraint compared to rats infused intracerebroventricularly with saline (40). It is clear that B infused directly into brain does not inhibit but rather excites both basal and stressor-induced ACTH secretion. These findings bolster the interpretation that GCs provide chronic inhibitory feedback from the periphery, whereas they are chronically excitatory in brain.

Evidence for peripheral energetic feedback mediated by B led us to investigate its potential sources. Reexamination of data from our previously reported or unpublished studies again showed the very strong negative relationship between the amount of sucrose consumed and CRF mRNA in the PVN (Fig. 5 *Left*). The data also show a significant, consistent negative

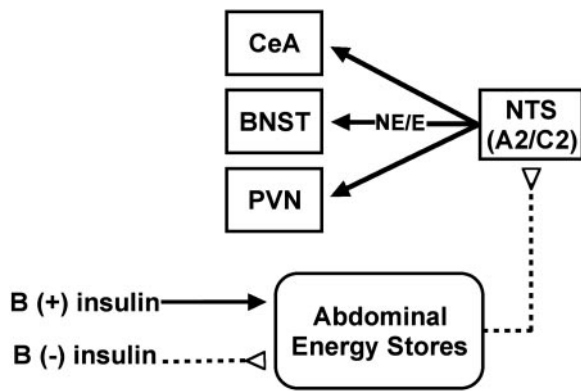


Fig. 6. Minimal working model of the actions of B on metabolic feedback of CRF and ACTH secretion. In the presence of food intake and insulin secretion, B stimulates accretion of abdominal energy depots. By contrast, without adequate food intake and insulin secretion, there is loss of energy stores. A signal of abdominal energy stores (to date unidentified) acts to inhibit noradrenergic (A2) and adrenergic (C2) norepinephrine (NE)- or epinephrine (E)-synthesizing neurons in the nucleus of the tractus solitarius (NTS). Catecholaminergic neurons innervate all three CRF-containing structures, the central nuclei of the amygdala (CeA), the bed nuclei of the stria terminalis (BNST), and the hypothalamic PVN.

correlation between mesenteric fat mass and CRF mRNA in the PVN (Fig. 5 *Right*). All points shown in Fig. 5 are from adrenalectomized rats without B replacement, drinking either sucrose or saccharin in addition to saline, or only saline. However, in every study in which we have measurements of mesenteric fat weight together with hypothalamic CRF mRNA, from either adrenalectomized or from intact rats, there is a consistent, significant negative correlation between mesenteric fat weight and CRF expression in the PVN. In contrast, there is no relationship between s.c. fat weight and CRF mRNA content in the PVN in any experiment (data not shown). These results suggest strongly that mesenteric (but not s.c.) fat stores serve as a signal of energy stores that feed back to inhibit CRF activity in the HPA axis.

In their totality, these studies suggested the new model of chronic corticosteroid effects shown in Fig. 1 *Right*. In the brain, chronic GCs feed forward to stimulate the HPA axis. In the periphery, GCs stimulate accretion of mesenteric energy stores. The central energy stores (exemplified by mesenteric WAT mass) provide a to-date-unidentified feedback signal to brain to reduce activity in the HPA axis. Fig. 6 shows our working model of the metabolic feedback on brain. As the abdominal energy-generated signal increases, the negative input to the A2/C2 catecholaminergic cells in the nucleus of the tractus solitarius reduces the synthesis of enzymes required for catecholamine synthesis; this result also occurs in A6 (LC). The decreased noradrenergic signal to the mpPVN (41), in turn, decreases CRF synthesis and secretion. Thus, there is a powerful metabolic feedback control of CRF in the PVN. The inhibitory metabolic signal of high abdominal energy stores does not appear to affect CRF mRNA in the amygdala.

GCs Act on Brain to Increase Stimulus Salience

Another key effect of GCs on the central nervous system appears to be to increase the compulsive nature of some activities. Clearly this is true for drug taking behaviors (42, 43), but it also seems to be true for other salient activities. Normal, intact rats voluntarily use running wheels consistently and will run miles each night, whereas adrenalectomized rats do not use running wheels, unless replaced with dexamethasone (44). Running was reinstated in adrenalectomized rats in proportion to the dose of

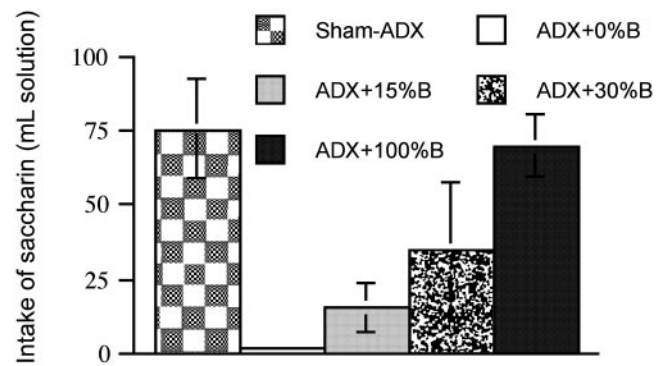


Fig. 7. B increases salience of the pleasurable drink, saccharin. Sham-operated or adrenalectomized rats with varying B treatments were allowed to drink saccharin for 9 days in a 15-day experiment. The data shown represent drinking on the last day of the experiment (38).

B treatment, and high concentrations of steroid that could occupy brain GC receptors were required for running to achieve the levels observed in intact rats (45). Similarly, intact rats drink a good deal of saccharin, whereas adrenalectomized rats drink very little. Both are consistent in their intake (Fig. 7 and ref. 38). Again, with increasing B replacement of adrenalectomized rats, saccharin ingestion increases in a strictly dose-related fashion, and it requires high concentrations of the steroid to restore drinking in adrenalectomized rats to those observed in intact rats (38). We have recently found a similar dose-related effect of B in adrenalectomized rats voluntarily ingesting lard; high concentrations of the steroid are required to restore fat eating to the levels observed in intact rats (S.E.I.F. and M.F.D., unpublished data). Thus, like the effects of B on drinking sucrose, but not eating chow (Fig. 4), stress levels of B specifically increase consumption of what may be called “comfort food,” that is, palatable foods, the sensory qualities of which indicate calories.

When the B-related response to saccharin is examined in ADX rats, both s.c. and mesenteric fat weights increase, although food intake does not. By contrast, when the comfort food is nutritious (sucrose and lard), mesenteric but not s.c. fat depots increase in weight with increasing B concentrations (Fig. 4). This comfort-food consumption occurs at the expense of chow intake in adrenalectomized rats infused with B directly into a cerebral ventricle (40). Similar effects occur in intact rats exposed to the chronic stressor of cold: more sucrose is ingested in cold, but less chow is eaten, provided that B concentrations are in the stress range that occupies brain GC receptors (46).

Experiments of others also imply that central CRF expression after stress is decreased by provision of preferred foods. Exposed to a variable stress paradigm with high-energy (high sucrose and fat) diets for 30 days, rats resistant to diet-induced obesity had elevated CRF mRNA in the PVN, whereas rats sensitive to diet-induced obesity did not exhibit increased CRF (47). Furthermore, rats exposed to inescapable tail shock 24 h before a shuttle-box avoidance test performed more poorly than controls. However, if they drank concentrated dextrose solutions during the night after inescapable shock and maintained their caloric intake and body weight, they performed like the control rats that were only restrained (48). This immunizing effect was not observed if nonnutritive saccharin drinking was allowed (49, 50).

Taken together, these studies suggest strongly that stress levels of GCs act in brain to increase the salience (51) of activities associated with seeking (e.g., wheel running), organize defensive responses, and modify consummatory aspects of nutrient ingestion (sucrose and fat). Moreover, they show that high B concentrations induce ingestion of comfort food when rats are simultaneously stressed. Thus, three important chronic proper-

ties of GCs are to increase CRF activity in the central nucleus of the amygdala, increase stimulus salience, and increase abdominal obesity, which then increases the metabolic inhibitory feedback signal on CRF mRNA in the mpPVN and reduces HPA activity. Evolutionarily, major circuits of brain are devoted to staying alive and finding food and mates. Persistently high concentrations of GCs act in three ways that are functionally congruent to two of these ends. They achieve continued responsiveness in the behavioral, autonomic, and neuroendocrine outputs of the chronic stress-response network, while also stimulating incentive salience to find a way out of the problem, and reducing further activity in the HPA axis by increasing abdominal energy stores.

Do the Effects of Chronic Stress and GCs in Rats Apply to Humans?

We believe the answer to this question is a resounding “yes!” Disordered eating syndromes [bulimia and night-eating syndrome (52)] consist of overeating calories in a bingeing fashion. Those with disordered eating, whether it be bingeing or ingesting most of the daily calories during the night, generally characterize themselves as chronically stressed (52, 53) and are obese. The foods that are overindulged-in typically have high fat and carbohydrate caloric content and may be characterized as comfort food. GC concentrations in these patients are slightly but not markedly elevated (54, 55). In contrast, patients with anorexia nervosa have very high cortisol concentrations and very low insulin concentrations but still have a decreased ratio of s.c. to abdominal fat stores as indicated by computed tomography (56, 57). High rates of depression are found in both groups. It seems possible that a major difference between disordered eating syndromes and anorexia nervosa is that people with the former are trying to make themselves feel better by reducing hypothalamic CRF activity by increasing their metabolic negative feedback signal. However, anorexics may be locked-in to seeking or escape modes of an emergency phenotype associated with starvation. It will be interesting to determine the extent to which the lower GCs in those with disordered eating vs. anorexia reflect a feeding-induced suppression of the HPA axis. Based on our model, eating comfort food would be expected to reduce activity in the HPA axis.

The American Psychiatric Association’s Diagnostic and Statistical Manual IV lists nine criteria, five of which must be met, for a diagnosis of depression. Of these, three sets are opposite pairs: weight gain/weight loss, hyperphagia/hypophagia, and hypersomnolence/insomnia. Generally, the first of each pair

accompanies a diagnosis of “atypical depression,” whereas the second accompanies a diagnosis of “melancholic depression” (58, 59). In young women, both groups have only slightly elevated circadian ACTH and cortisol concentrations (60). However, in an older male depressed population and in elderly males and females, the HPA axis is disturbed, particularly in those with melancholic depression (61–63). Moreover, cerebrospinal fluid samples from patients with atypical and melancholic depression indicate that atypical depressives have normal CRF and catecholamine concentrations, whereas melancholic depressives have abnormal elevations in both (58, 64, 65). Again, it may be that those who gain weight, overeat, and sleep more when depressed [or anxious (59)] are trying to feel better through comfort food. It is provocative that an unwanted side-effect of antidepressant drugs is obesity (66).

Although the above examples suggest that some people with psychiatric diagnoses overeat when stressed, it is not necessary to have overt psychiatric problems to use comfort food for consolation when feeling down and out. In highly developed countries, this is a well recognized and general occurrence, with a consequent epidemic of obesity (67). There is no doubt that eating high fat and carbohydrate comfort foods cheers people up and may make them feel and function better (68). In people, feeling better may result, as in rats, from reduction in central CRF expression and the resulting dysphorias. However, habitual use of these foods, perhaps stimulated by abnormally elevated concentrations of cortisol as a consequence of underlying stressors, results in abdominal obesity. Unfortunately, this particular type of obesity is strongly associated with type II diabetes, cardiovascular disease, and stroke. In the short term, or in societies where there is not immediate and continual access to comfort foods, occasional relief of anxiety with sweet or fatty foods is probably useful. Habitually attempting to relieve the stress-induced dysphoric effects of the CRF-driven central chronic stress-response network may make one feel better, but it is likely to be bad for long-term health.

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