Journal of Neuroendocrinology, 2001, Vol. 13, 827–835

YOUNG INVESTIGATOR PERSPECTIVES

A New Perspective on Glucocorticoid Feedback: Relation to Stress, Carbohydrate Feeding and Feeling Better

Kevin D. Laugero
Department of Physiology, School of Medicine, University of California San Francisco, San Francisco, CA, USA.

Keywords: CRF, HPA axis, sucrose ingestion, energy balance, model.

Abstract

Input to and regulation of activity in the hypothalamic-pituitary-adrenal (HPA) axis is diverse and complex. Glucocorticoid feedback is a major component that determines activity in this classic neuroendocrine axis and, while feedback occurs through the brain, the pathways that mediate glucocorticoid feedback remain unknown. In this review, I discuss findings that have led us to view glucocorticoid feedback in the HPA axis in a new light. Much of what has precipitated this view comes from a very surprising finding in our laboratory; sucrose ingestion normalizes feeding, energy balance and central corticotropin releasing factor expression in adrenalectomized (ADX) rats. Since this discovery, a diverse set of literature that supports this view of glucocorticoid feedback has been found. Taken together, recent findings of the well-known importance of glucocorticoids to feeding and energy balance, and the modulatory actions of carbohydrate ingestion on both basal and stress-induced activity in the HPA axis, strongly suggest that many metabolic (e.g. obesity) and psychological (e.g. depression) pathologies, which often present together and have been associated with stress and HPA dysregulation, might, in part, be understood in light of our new view of glucocorticoid feedback.

Hypothesis

Our working hypothesis is that, in the basal state, glucocorticoids primarily act in the periphery to affect energy balance, and these metabolic actions mediate the effects of the steroid on brain corticotropin releasing factor (CRF) systems. CRF activity, in turn, has tremendous influence over behavioural (e.g. feeding), neuroendocrine (e.g. hypothalamic-pituitary-adrenal, HPA) and neural activation (e.g. sympathetic nervous system, SNS). Throughout, I emphasize the effects of carbohydrate ingestion on activity in the HPA axis during both stress and basal states to demonstrate the rationale for the hypothesis of glucocorticoid feedback. Reasons for focusing on the effects of carbohydrate feeding include: (i) glucocorticoids are named for their critical role of maintaining carbohydrate (glucose/glycogen) balance; (ii) glucose is the primary energetic substrate utilized by the central nervous system (CNS) and is not stored to any appreciable degree; (iii) availability of simple carbohydrates, such as sucrose, provide a highly energetic, immediate and utilizable substrate that seems to be important during times of stress (1, 2); and (iv) in a 'fat-free' crazed society, the 'trade-off' has been to increase ingestion of the highly palatable, carbohydrate-dense foods. The dietary switch, incidentally, has not apparently reduced the incidence of obesity or diabetes (3).

Below, I briefly outline the general components and function of the HPA axis. I then provide an overview of the modulatory effects of carbohydrate feeding on both basal and stress-induced activity in the HPA axis. Finally, I present my perspective on glucocorticoid feedback under basal conditions and how this new view of glucocorticoid feedback might explain the behavioural and metabolic consequences of ingesting carbohydrate under states of stress.

HPA axis

The HPA axis is a well-known and characterized neuroendocrine system (4). It is a classic feedback system, whereby CRF and, under certain conditions, arginine vasopressin (AVP), are

Correspondence to: Kevin D. Laugero, Department of Physiology, Box 0444, UCSF, San Francisco, CA 94143-0444, USA (e-mail: laugero@itsa.ucsf.edu).

synthesized in parvocellular neurones in the parventricular nucleus of the hypothalamus and secreted into the hypophyseal portal system, reaching the anterior pituitary, and stimulate synthesis and secretion of adrenocorticotropin (ACTH) into the systemic circulation. ACTH then stimulates corticosteroid synthesis and secretion from the adrenal gland. Therefore, each level of the axis generally reflects the others. Glucocorticoids, in turn, act through brain to inhibit drive to the CRF neurone and activity in the HPA axis.

The HPA axis serves multiple functions, which are contextually dependent. However, common to all the apparent functions, is the regulation of glucocorticoid output. It is the action of glucocorticoids that result in altered cellular activity and function under both basal and stressful conditions. Glucocorticoids modulate neural systems that control learning and memory (5, 6), feeding (7), ingestion of sweet solutions (8, 9), autonomic outflow (7–9) and activity in the HPA axis (4). These functions are revealed by the effect of adrenalectomized (ADX) and glucocorticoid replacement. ADX alters brain CRF and norepineprine activity (10, 11), increases ACTH secretion (4), sympathetic outflow (8, 9) and disrupts behaviour [e.g. wheel running (12), drinking sweets (8, 9) and feeding (7)]. All of these disruptions are corrected by glucocorticoid treatment. Many of these behavioural, neuroendocrine and autonomic consequences might be explained by the altered CRF activity that accompanies ADX (see below).

Activity in the HPA axis is also instrumental to energy flow (mobilization, storage). During the basal, nonstressed state, HPA function seems to reflect its circadian dynamics. In man and in rodents, activity peaks just prior to waking, increased activity and feeding (13). This fact underlies the hypothesis that increased glucocorticoid secretion may be important to the mobilization of energy that is required to support the ensuing increase in activity, probably related, in large part, to foraging behaviour (14). Furthermore, glucocorticoids are unquestionably critical to normal feeding, and this effect may be a direct or indirect action of the steroid on neuropeptide Y (NPY) (15). In fact, glucocorticoid removal inhibits feeding (7) and activity (12), but ADX animals do maintain a diurnal rhythm of feeding (16). Furthermore, if rats are trained to eat on a schedule, the time of corticosterone peak shifts such that it precedes the feeding time, not necessarily following a light cue (17). As their name implies, glucocorticoids stimulate glucose output from the liver by inducing gluconeogenic enzymes and by mediating, through their catabolic action on muscle, the provision of gluconeogenic substrate. In terms of energy storage, glucocorticoids are required for a normal insulin response (15), and stimulate glycogen storage (18) and lipogenesis (19). Glucocorticoid removal inhibits, and replacement restores, energy storage.

Carbohydrate feeding, stress and the HPA axis

CRF expression in the paraventricular (PVN) and amygdala is normalized in ADX rats when they drink sucrose (Fig. 1) (20). We also observed that sucrose, but not saccharin, ingestion restores caloric intake, efficiency and storage in ADX rats (Fig. 2); circulating triglyceride, insulin and leptin were also normal (20). Carbohydrate ingestion has also been shown to modulate the response to many types of stressors and stress-related behavioural states. For example, inescapable foot shock depresses saccharin drinking, but increases sucrose ingestion (21). This behaviour blocks the stress-induced inhibition of body weight (1, 21). Furthermore, Minor *et al.* (22) showed that glucose ingestion blocked the behavioural impairment (learned helplessness) of rats exposed to the inescapable shock model.

The HPA response to stress was attenuated in rats consuming a high caloric and/or carbohydrate diet (23, 24). Additionally, sucrose, but not saccharin, diminishes the quantity of morphine rats self-administer in a pain/tolerance paradigm (25), an effect not due to protein or micronutrient shifts (26). In man, eating after stress exposure was shown to increase caloric intake on the day of stress with a preference for sweet food (27). Similarly, provision of a high carbohydrate diet to human subjects before experimental stress also inhibits cortisol and feelings of depression after stress (28). Finally, carbohydrate loading prior to prolonged exercise has been shown to increase performance and reduce the normal rise in cortisol (29). Therefore, there is a rich and diverse series of studies that clearly demonstrate the modulatory actions of carbohydrate intake on the basal and neuroendocrine, metabolic and behavioural responses to stress.

A new glucocorticoid feedback system

While glucocorticoids are, unquestionably, required for maintenance of basal CRF and HPA activity, the brain site through which the steroid acts remains unidentified. Our findings in sucrose-drinking ADX rats strongly suggest that, under basal conditions, the CRF systems are primarily under the control of energy storage dynamics, a glucocorticoid-sensitive function (Fig. 3). Therefore, it appears that basal glucocorticoid feedback is not a consequence of the direct actions of the steroid on brain. Since, under both stress and ADX conditions, rats prefer sucrose to saccharin and since glucocorticoids play a critical role in caloric flow (mobilization; deposition), it is reasonable to believe that, under basal conditions, glucocorticoid feedback is a consequence of the metabolic actions of the adrenal steroid, not a direct effect on brain. Furthermore, ADX animals maintain a diurnal ACTH and CRF (expression) rhythm (4, 30) and, when fasted overnight, maintain a normal increase in ACTH (31). Furthermore, if ADX rats are gavage-fed during this period, the ACTH response is attenuated. Finally, stress-induced activity in the HPA axis is determined by a larger system that mediates feeding and energy flow, and this regulatory program is maintained in ADX animals (15). Therefore, these together with the results presented above, suggest that glucocorticoid feedback in the HPA axis depends on some aspect(s) of energy balance. If our hypothesis is true, anything that alters energy balance, whether it be before, during or after stress, might alter HPA and other glucocorticoid-sensitive sites in the CNS (e.g. amygdala). Interestingly, many of these sites that have been thought to modulate the HPA axis also appear to play a role in some aspect of energy balance (insulin secretion, SNS output, body weight maintenance, feeding) (32).

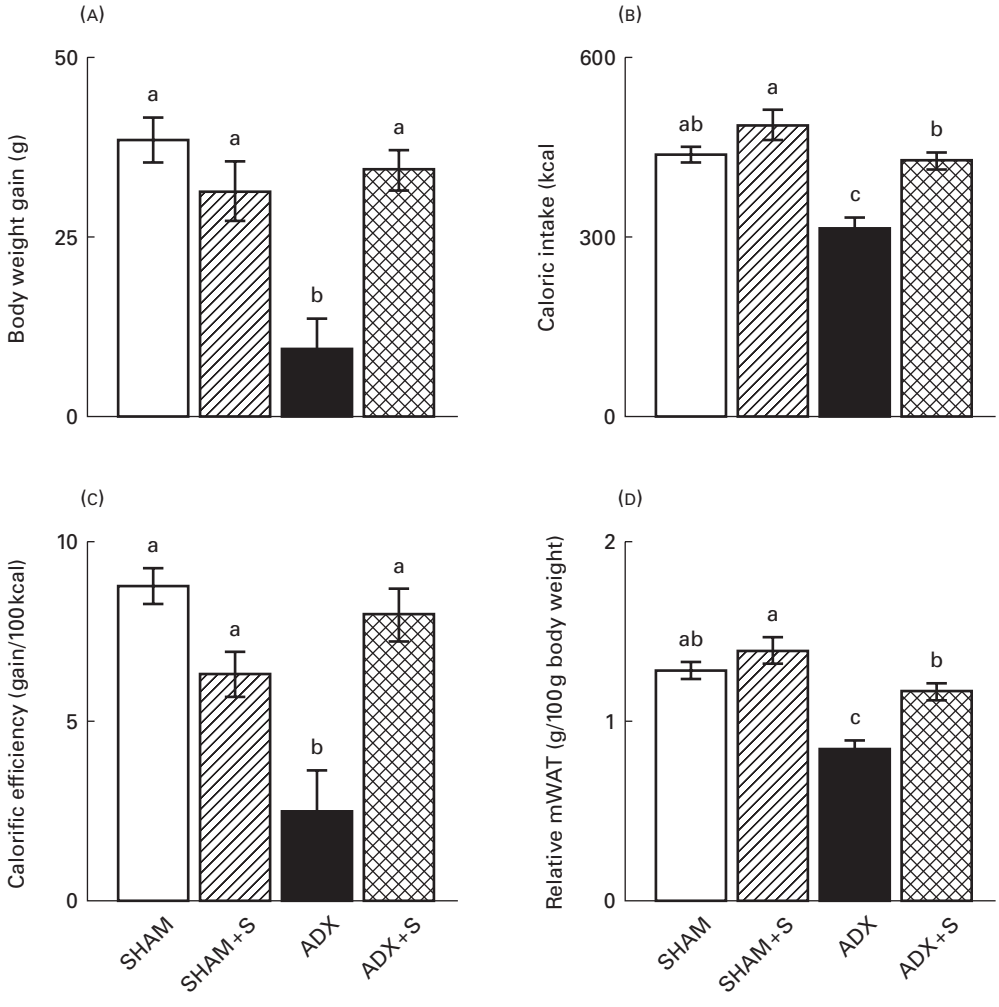

FIG. 1. Adrenalectomy increased corticotropin releasing factor (CRF) mRNA expression in the PVN relative to shams (SHAM). While the mean CRF mRNA expression in adrenalectomized (ADX), sucrose-drinking rats (ADX + S) was not different from that of ADX rats drinking saccharin or only saline in the 5-day study, the variance was essentially explained by the amount of sucrose drunk over the last 24 h in ADX rats (B, C). Comparison of the results from rats drinking only saline, and those allowed saccharin as well, showed that saccharin had no effect; therefore, the results were pooled (ADX). Adapted with permission (31).

Implications to feeding behaviour and feeling better: role of maintaining central CRF tone

Overall, this glucocorticoid–body–brain axis provides an alternative mechanism through which glucocorticoids impart their centrally active effects under basal conditions. Since this work has emphasized the interaction between feeding and the HPA axis, I next discuss the implications of the described glucocorticoid feedback system to the regulation of normal feeding. The HPA axis is largely unappreciated as a major regulator of daily, basal food intake, but there is no question that normal feeding requires glucocorticoid input.

Rats prefer carbohydrate during their first major feeding bout (just after lights out) and glucocorticoid loss reduces carbohydrate intake disproportionately, compared to fat and protein; type II glucocorticoid receptor agonists restore the normal preference pattern (33). PVN lesions also decrease carbohydrate preference at lights out (34), and the central α_2-noradrenergic-induced increase in preferential carbohydrate feeding is blocked by ADX and restored by glucocorticoid replacement (35). Furthermore, NPY also peaks just prior to the diurnal feeding period, and this diurnal rise is seen in the PVN (36). NPY stimulates feeding (7) and the HPA axis (37). However, these two effects of NPY may be dissociated (38). NPY also appears to be especially important to carbohydrate intake and energy balance; e.g. NPY increases RQ, insulin, preferred glucose uptake in adipocytes, decreases energy expenditure, and increases lipogenesis and preferred carbohydrate feeding (7, 39). Moreover, ADX blunts the feeding response to NPY (40), and many of the NPY-induced peripheral effects are glucocorticoid-dependent (11, 41). Together, the HPA axis and hypothalamic NPYergic cell groups appear to respond to energetic deficits and integrate a feeding and metabolic response that insures

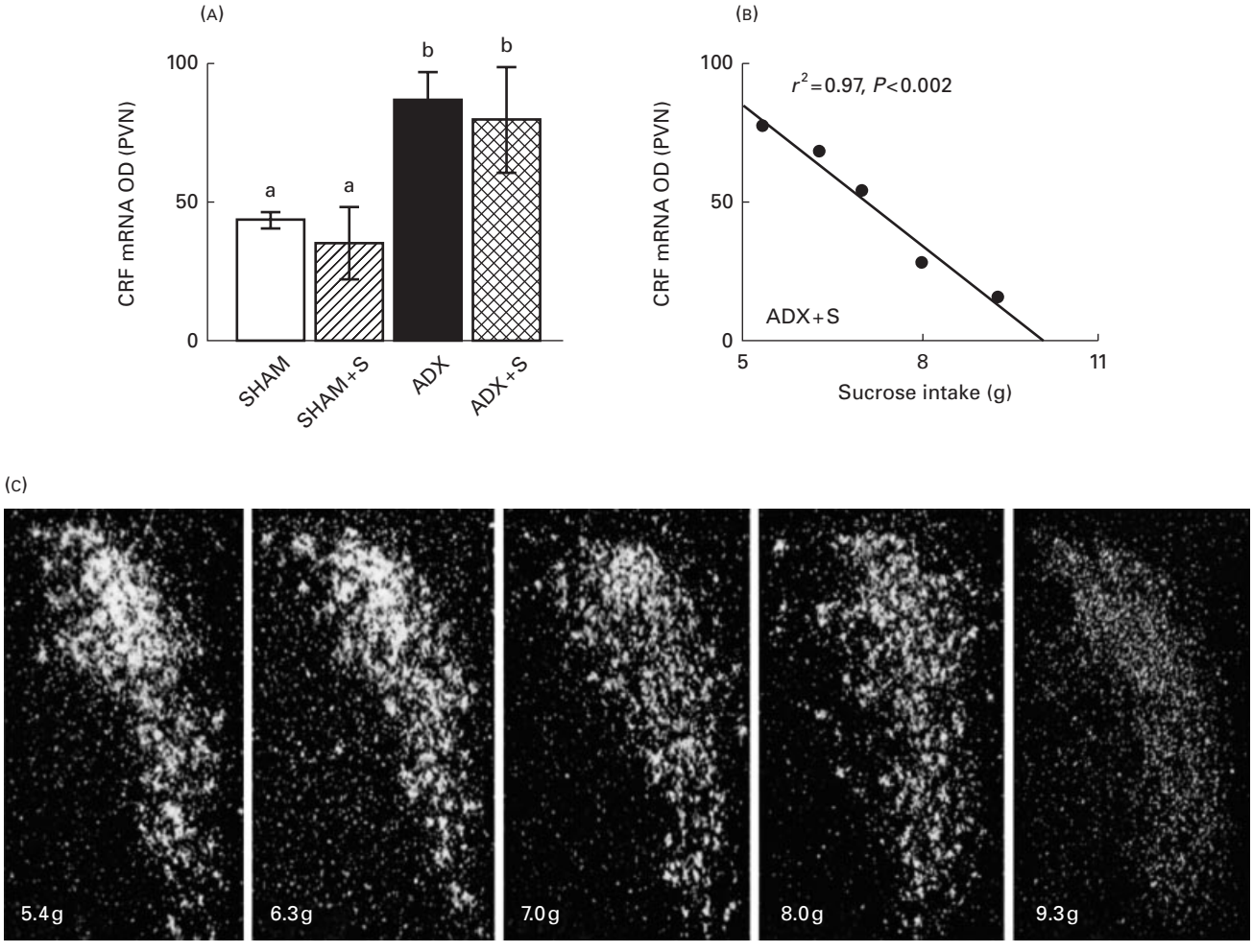

FIG. 2. Sucrose (ADX + S) consumption by adrenalectomized (ADX) rats restored total (A) body weight gain (g), (B) caloric intake (kcal) and (C) caloric efficiency (mg body weight gain/kcal intake) to normal. All variables represent the net quantity over the 5-day study. Adapted with permission (31).

carbohydrate intake and energy balance. It should be noted, however, that feeding in NPY-knockout mice is not significantly altered (42). However, this lack of effect might be related to the fact that adrenalectomy also fails to alter feeding in mice (43). Furthermore, with any knockout manipulation, critical functions such as feeding should have multiple and overlapping modulators that insure its capacity.

In line with these findings, a model that incorporates NPY and the HPA axis as important regulators of food intake has been put forth by Dallman *et al*. (15), which has since been supported by Strack *et al*. (44). In this model, glucocorticoids stimulate and insulin inhibits feeding through their actions on hypothalamic NPY activity. In the periphery, the effects of these hormones on energy storage are opposite. However, glucocorticoids stimulate insulin secretion and, consequently, energy storage if food is consumed. Although the stimulatory effects of glucocorticoids on feeding have been assumed to be mediated by their direct actions on hypothalamic NPY neurones, there is an equally plausible mechanism that encompasses our glucocorticoid–body–brain feedback model. Since ADX blunts the normal feeding response to NPY injections, glucocorticoids must have their feeding effects, at least in part, through another pathway. I believe that control of central CRF activity (through glucocorticoid feedback) is a major avenue through which glucocorticoids influence feeding behaviour in nonstressed animals.

ADX dramatically alters CRF activity in brain sites known to modulate and respond to feeding (e.g. PVN; central amygdala). Furthermore, i.c.v. CRF inhibits feeding (45) and CRF antagonists block the stress-induced inhibition of food intake (46). It is apparent that CRF influences behavioural, neuroendocrine, autonomic and metabolic function. Administration of CRF in nonstressed animals results in stress-like alterations: reduced feeding, increased energy expenditure, HPA and SNS activation and reduced activity, and has been shown to cause states resembling anxiety and depression (45). CRF antagonists inhibit or attenuate many of these consequences of stress (47), and thus this neuropeptide is believed to mediate the response to many stressors. CRF-expressing neuronal cell groups, such as the PVN and amygdala, are modulated by glucocorticoids; the steroid influences mRNA and peptide expression of CRF in these nuclei (48, 49). Finally, similar to ADX, increased CRF precludes the normal stimulatory effect of NPY on feeding behaviour (50), and

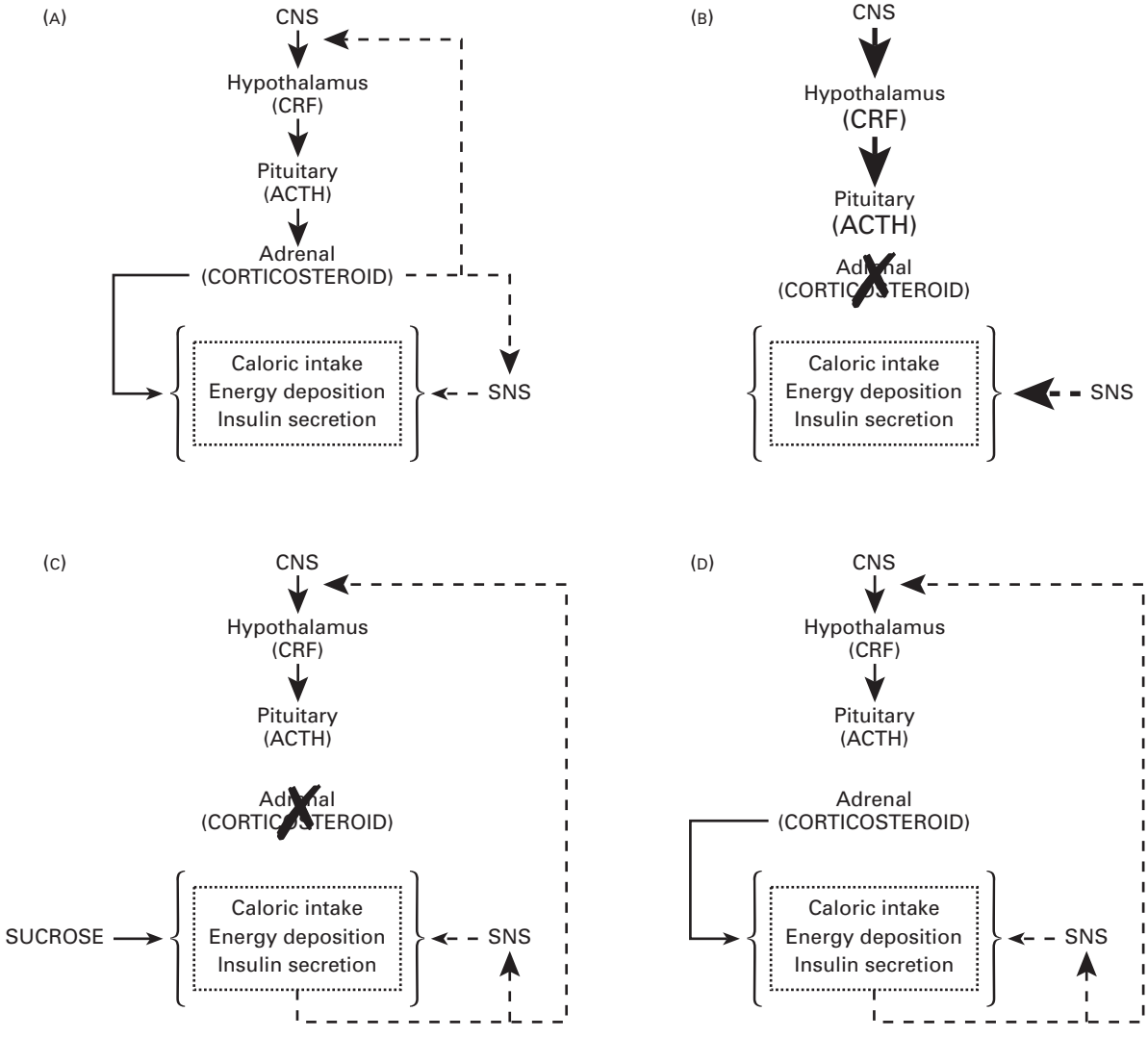

FIG. 3. Glucocorticoid feedback effects on basal activity of the hypothalamic-pituitary-adrenal (HPA) axis have been assumed to be exerted by the steroid's direct actions on brain (A). Under basal conditions, glucocorticoids are also required for normal sympathetic nervous system (SNS) and energetic function. Removal of the adrenal steroid via adrenalectomy increases activity of the HPA and SNS systems and reduces metabolic function (B). However, drinking sucrose prevents all of these adrenalectomized (ADX)-induced neuroendocrine, autonomic and energetic disruptions (C); the suppressive effects of glucocorticoids on basal HPA axis and SNS output may be due to the metabolic effects of the sterois in the periphery, i.e. a glucocorticoid-metabolic-brain feedback loop (D). The input to each level in the model is depicted by an arrow. Arrow size indicates the net drive. Solid lines are stimulatory; dashed lines are inhibitory. Cross through text indicates adrenalectomy.

CRF antagonists and inactivation potentiate the effects of NPY on feeding (51).

In addition to the energetically driven motivation to eat, the reward that comes with feeding, especially palatable foods such as sweet carbohydrates, contributes to feeding drive (52); hence, the balance between energetic need and reward drive feeding behaviour (52). CRF also influences reward-induced feeding (52). The opioid system is believed to provide the hedonic/pleasure aspects of food intake (*liking*) (53) while the dopaminergic system mediates the incentive salience aspect of feeding (*wanting*) (53). Of course, it is important to realize that these systems should integrate both the gustatory and metabolic consequences of eating. For example, if there arises a condition that demands replenishment of some energetic state, it does not make sense to consume a palatable, but non-nutritive substance (e.g. saccharin). Indeed, as I have described, animals that are ADX or stressed prefer to ingest sucrose compared to saccharin. The hedonia that comes with ingesting food such as sucrose might increase the propensity of an animal to eat, particularly when they do not 'feel' hungry (increased CRF, reduced NPY effects). This may explain why ADX animals fail to consume normal amounts of regular chow (and calories) but, if given access to sucrose, ADX animals consume normal calories by ingesting sucrose, in addition to chow. Furthermore, the availability of simple carbohydrates, such as sucrose, provides a highly energetic, immediate and utilizable substrate that seems to be important during times of stress or in conditions where the

ability to respond to future stressors is compromised (e.g. glucocorticoid insufficiency). During these situations, the general suppression of feeding may be adaptive and energy conserving. However, the reward-induced drive to consume palatable substrates such as sucrose (when available) might insure survival (54) and prevent the negative effects of reduced feeding.

It might be imagined that, under the nonstressed state following the normal diurnal period of relative fasting, some aspect of energy balance (e.g. reduced glucose and/or fat storage) induces activity in the HPA axis and the drive to 'forage' and feed to replenish these stores. These signals of energy deficit stimulate CRF expression in the hypothalamus, which in turn stimulate glucocorticoid output. In turn, increased glucocorticoids stimulate the mobilization of endogenous energy stores to insure the maintenance of circulating glucose in case food is not consumed and to support the increased 'foraging' activity that ensues. The parallel rise in NPY increases appetite and, if feeding occurs, insulin is secreted and energy balance is replenished. This restoration of energy balance, in turn, feeds back on brain to inhibit CRF in the hypothalamus. If the glucocorticoid-induced metabolic shifts are inadequate (e.g. during ADX), there is increased drive to PVN CRF neurones and increased CRF activity. Increased CRF activity in the PVN suppresses the drive to eat (maybe by inhibiting the action of NPY), increases sympathetic outflow and may result in feelings of depression or anxiety. Thus, glucocorticoid feedback acts to modulate brain CRF, and it is through this function that the systems driving normal feeding are capable of carrying out their function. Therefore, in terms of regulation of energy balance, glucocorticoids act primarily to insure energy availability (mobilization and storage), which in turn mediates the feedback of steroids on central CRF activity. The dynamics of CRF determine whether normal feeding behaviour occurs. As shown in Fig. 4, this model might explain the effects of ADX and sucrose feeding.

While the above model of feeding attempts to explain the basal condition by extrapolating from the ADX condition, this model provides a means to understand the metabolic and psychiatric consequences of feeding under chronic stress or any condition that alters central CRF (e.g. depression). Stress inhibits feeding and stimulates mobilization of endogenous energy stores that, with time, can become detrimental to the organism. Feeding during times of chronic stress would presumably help attenuate energetic deficits, and these peripheral deficits might be manifested as 'feelings' that we have consciously labelled depression (55). Food intake (especially of palatable foods) is considered to be pleasurable (52), which is probably the result of a reinforcement mechanism that integrates both the gustatory (taste) and metabolic consequences of feeding behaviour. Thus, an underlying mechanism that might increase the likelihood of reducing the negative energetic effects of chronic stress is pleasure seeking to counter the stress-induced affective state. The well known modulatory effects of glucocorticoids on CRF systems, and our glucocorticoid–body–brain feedback model, explain how feeding during these times of chronic stress might attenuate disrupted CRF activity and the behavioural and affective consequences that come with an altered CRF circuitry (Fig. 4).

The voluntary ingestion of carbohydrate-dense foods obviously has modulatory effects on the stress response in animals and man (above). It is possible that this behaviour is a response to the negative feelings that come with stress or depression. In the demonstration that stress increased caloric and, especially, sweet food intake in humans (27), the propensity to eat after stress was related to increased negative mood scores. Depression has also been shown to increase the craving for sucrose in man and animals (56). Moreover, patients with night-eating-syndrome show hyperphagia and insomnia in the evening, with the bulk of their calories coming from carbohydrate (57, 58). These individuals hypersecrete cortisol and have lower mood scores, particularly towards the later part of the evening when they consume most of their daily calories. Furthermore, some depressed people (atypical) overeat, sleep more and are lethargic and fatigued (59). Finally, food binging behaviour reduces feelings of stress in bulimics (60). Bulimia is also characterized by a dysregulated HPA axis (61), and 'reversed depression' has been correlated with reduced cortisol in bulimic patients (62). In each of these cases, disrupted brain CRF and HPA activity are thought to contribute to the affective states (63). Therefore, from our discussion of the effects of carbohydrate on the response to ADX and stress, it is possible that some individuals find that it 'feels' better (55) to ingest carbohydrate. The incentive for the feeding behaviour might be to counter the 'ill feeling' that comes with chronic stress or depression, and these 'feelings' might really be extensions of the metabolic derangements that accompany these syndromes.

Sucrose restores energy balance in ADX rats. Furthermore, ADX and stress induce a preference for sucrose over saccharin (20, 21), even though basal consumption does not differ. In fact, recordings from the neural gustatory neurones suggest that gustatory responses to sucrose and saccharin fail to distinguish between the two sweets (64). Therefore, there appears to be a shift in preference that insures ingestion of a nutritive substance, which in turn, reduces the potentially harmful metabolic consequences. Furthermore, stress, depression and ADX alter metabolism to a large degree and, if chronically engaged, these metabolic shifts can have serious consequences to the organism (20, 46, 65, 66). Therefore, these results imply that the positive effects of sucrose on energy balance modulate the central mechanisms that control behaviour, and possibly affect.

Finally, there is a potential trade-off to this type of self-treatment, if chronic. Feeding, during times when glucocorticoids are high, also stimulates insulin secretion (15). Together, the increase in both hormones may ultimately result in a remodelling of energy stores from muscle to fat, especially to the abdominal region (15, 67). Thus, although one might feel better through eating, there may ensue an increased risk of developing obesity (66, 68) and obesity-related diseases (cardiovascular, diabetes), since these diseases are especially associated with abdominal obesity (67, 69).

There is another consequence that becomes evident when considering major depression. There are two major types of this disorder: atypical and melancholic. Melancholic depression is characterized by anhedonia, weight loss, insomnia,

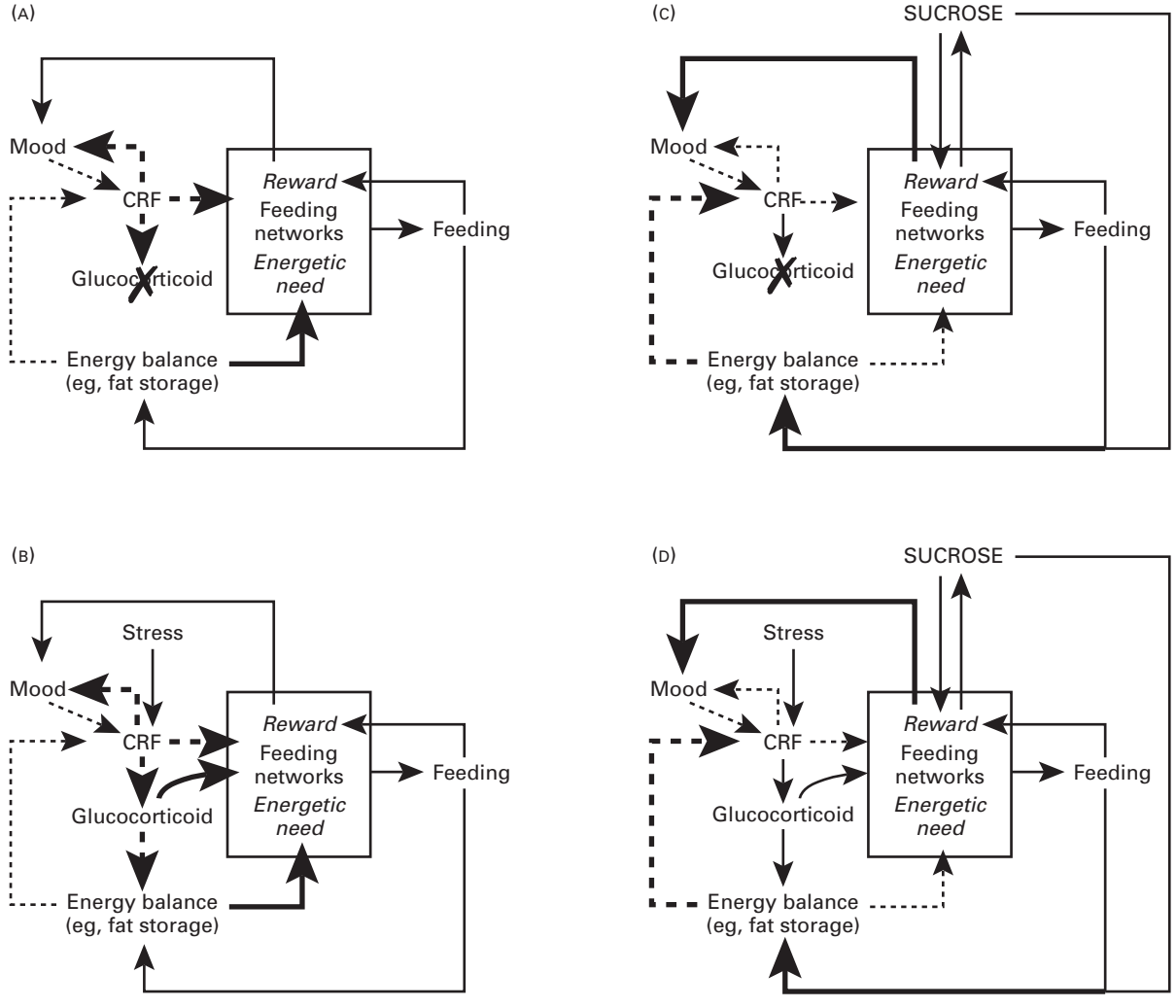

FIG. 4. Speculative model depicting the relationship between our view of glucocorticoid feedback (see Fig. 3), feeding, stress, adrenalectomy (ADX) and sucrose ingestion. Glucocorticoids induce important metabolic shifts during the basal and stress states. These shifts insure energy availability. ADX (A) and chronic stress (B) can lead to inadequate or prolonged metabolic shifts and abnormal energy balance, which in turn stimulate corticotropin releasing factor (CRF). Increased CRF activity inhibits food intake and alters mood (e.g. depression). However, when available, ingestion of highly palatable, rewarding and nutritive substrates (sucrose) might overcome the CRF-induced appetite suppression (C, D). The restored caloric intake normalizes metabolism and, consequently, CRF and mood. While this type of stress-induced feeding behaviour might acutely normalize energy balance and negative mood, repeated stress and carbohydrate eating might lead to obesity and obesity-related pathologies. Further details are provided in the text.

elevated CRF in cerebral spinal fluid and facilitated HPA responsivity (59). By contrast, atypical depression is characterized by weight gain, hypersomnia and depressed HPA responsivity (59). Thus, the atypical patients may be changing neuroendocrine function through eating, thereby altering their affective symptoms, at least for a time.

What does all of this mean?

Taken together, it appears that the glucocorticoid-dependent basal activity in the HPA axis, and probably in other CNS sites (e.g. amygdala), is mediated by the metabolic effects of glucocorticoids, as opposed to direct actions on these neuronal structures. Furthermore, it is possible that the effects of carbohydrate feeding on this neuroendocrine axis during stress, and possibly depression, are transmitted via this pathway. Animals are capable of making associations between the conditioned stimuli of food (e.g. taste) and its unconditioned consequence (e.g. postingestive effects) (70). In fact, there is evidence that rats can generate memories about the consequential qualities of ingesting specific macronutrients, such as carbohydrates and fats (70). Thus, depending on the specific context (i.e. glucoprivic versus lipoprivic state), rats will be more likely to demonstrate consumatory behaviour for the appropriate nutrient, when cued. In the case of the ADX animal, its capacity for endogenous glucose production is attenuated by the loss of glucocorticoids and, during stress, the animal's glucose requirements and endogenous production increase. Since both of these conditions suppress feeding, mobilization of endogenous energy stores become critical to the animal. In other words, increased activity in the HPA axis and, consequently, glucocorticoid secretion insures that the

energy demands induced during/after stress or by increased foraging at the circadian peak are met.

This may explain why stress and ADX stimulate a preference, or craving, for nutritive carbohydrates. The pleasurable consequence (reinforcement) that results from ingesting carbohydrate-rich food may serve to insure this type of feeding behaviour. When safe, feeding during and following stress might be physiologically adaptive and may be manifested through affect, thereby reinforcing the adaptive behaviour. The contribution of metabolic and rewarding aspects of carbohydrate ingestion to CNS modulation demands testing. Each may act in parallel to mediate the CNS effects of carbohydrate consumption, or they may interact. In fact, the behavioural state of mind that is driven by reward processes may simply be an extension of the state of body. Finally, while ameliorating the acute negative outcomes of chronic stress, repeated stress exposure and self-treatment of these stress-induced symptoms in this manner could easily produce other problems such as diabetes and obesity.

Acknowledgements

This study was supported by grants DK28172, T32 DK07418 (to K.D.L.) and F32 DK59735 (to K.D.L.).

Acceepted 2 July 2001

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