Invited minireview

Chronic stress and comfort foods: Self-medication and abdominal obesity

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Abstract

Central corticotropin-releasing factor (CRF) networks are recruited by chronic stressors and elevated glucocorticoids (GCs) that initiate recruitment of central CRF activity in the amygdala. Increased central activity of the CRF network stimulates all monoaminergic cell groups, as well as premotor autonomic and other limbic structures resulting in the typical arousal, behavioral changes, autonomic, and neuroendocrine changes that accompany the chronic imposition of a stressor. By contrast, elevated GCs appear, through a variety of means to counteract the effects of central CRF, which they have initiated. Together with insulin, the GCs stimulate drive for and ingestion of “comfort foods” that may directly result in reduction of the negative effects of the chronic stressor in the nucleus Accumbens, through stimulation of the anterior, more pleasure-associated part of this cell group, thus reducing the weight of the stress-stimulated posterior, more defensive part. Furthermore, the shift in caloric intake from chow to preference for “comfort foods,” together with elevated GCs and insulin, reorganize energy stores from a peripheral to a central distribution, primarily as abdominal fat. A signal associated with this fat depot appears, as with eating “comfort foods,” to reduce the influence of the chronic stress network on behaviors, autonomic, and neuroendocrine outflow.

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1. Introduction

The hypothalmo–pituitary–adrenal (HPA) axis is a prototype of neuroendocrine systems with inhibitory feedback loops mediated by the hormone secreted from a remote target gland. The HPA axis is stimulated by stressors (both physical and psychological insults), and exhibits a strong circadian rhythm that peaks just prior to the onset of the daily activity cycle. Its activity is inhibited by adrenal glucocorticoid secretion, in a “long-loop feedback.” In the 1950s, with new capability to measure circulating corticosteroid concentrations in humans and animals, it became abundantly clear that treatment with glucocorticoids (GCs) dramatically reduced the secretory capacity of the system from the hypothalamus (corticotropin-releasing factor; CRF) and from the anterior pituitary (adrenocorticotropin; ACTH). This recognition was in large part responsible for the routine extra ‘surgical coverage’ for individuals treated with life-saving GCs for other disease processes (Munck et al., 1984). However, most of the early experimental studies examined the effect of prior treatment with exogenous GCs on subsequent basal and stress-induced activity in the HPA axis. Under basal conditions, prolonged treatment with GCs does, indeed, inhibit most components of the HPA axis (Dallman et al., 1987).

However, when tests were made of the effects of stressor-induced, endogenous GC secretion, subsequent CRF and ACTH responses to novel stressors were not inhibited, although stress-induced GC secretion was sufficient to inhibit ACTH secretion to acute stress in the absence of concurrent stress (Dallman et al., 1987). GC feedback was ineffective in the presence of a stressor, and...
high concentrations were required in chronically stressed animals for a normal HPA response to a novel stressor. Exploration of the relationships among acute and chronic stressors, the brain and the HPA axis shows the following: (1) GCs act in a direct, feedback inhibitory mode to reduce the duration of any single episode of CRF and ACTH secretion; (2) GCs act directly in a feed-forward, excitatory or positive, mode on brain to increase drive, and CRF and ACTH secretion; (3) in the presence of insulin, stress, and GCs increase the relative intake of “comfort foods” and reduce HPA activity; and, (4) GCs act on peripheral energy storage organs to promote central obesity, providing an indirect, secondary inhibitory feedback signal that limits the degree of chronic stress perceived by the organism. Here we briefly review these effects and interactions of stress, GCs, drive, and metabolism.

1.1. GCs act in a direct, feedback inhibitory mode to reduce the duration of any single episode of CRF and ACTH secretion (Fig. 1, bottom left)

The ACTH response to an acute stressor is temporally limited is greatest shortly after the onset of the stressor and may return to basal concentrations during the sustained application of a mild stressor, such as tube-restraint, provided that GCs can be secreted endogenously or are infused. However, if the adrenals cannot secrete GCs and the steroids are not infused, ACTH responses to a stimulus are prolonged, and may persist for hours. The normal, acute rise in GCs that follow an ACTH response to a stressor acts on CRF neurons to inhibit a

1.2. GCs act directly in a feed-forward, positive mode on brain to increase food-associated drives, CRF and ACTH secretion (Fig. 1, bottom left middle)

These unexpected findings came from experiments that were designed to test other propositions. It is widely agreed that both stress and glucocorticoid treatment affect responses to drugs of abuse (Goeders, 2002; Koob and Le Moal, 2001). We used pleasurable, high-density sucrose (30%) as a drug-surrogate to test the effects of varied concentrations of corticosterone in adrenalectomized rats on the amount of sucrose drunk (Bell et al., 2000); we also tested the effect of corticosterone on saccharin intake (Bhatnagar et al., 2000). The amounts of both sweet drinks ingested by adrenalectomized rats depended on circulating corticosterone. Furthermore, adrenalectomized rats respond to corticosterone in a dose-related manner to engage in running-wheel behavior (Leshner, 1971) and in schedule-induced polydipsia (Cirulli et al., 1994), both of which are motivated behaviors surrounding food intake.

The corticosterone dose-related responses above are probably associated with the effects of corticosterone on

Fig. 1. Stress and glucocorticoids (GCs) act on brain to alter activity in various sites with varying effects. Bottom left to right: GC fast-feedback acts at the hypothalamus (PVN) and corticotrope cells of the anterior pituitary (a. Pit) to inhibit the duration of ACTH secretion in response to acute stress. GCs, in the presence of insulin, stimulate motivation for “comfort foods,” an action probably exerted in the meso-limbic dopaminergic system (VTA, ACC shell). Stress and elevated GCs activate the central CRF chronic stress network; high glucocorticoids stimulate CRF expression in the limbic central nucleus of the amygdala (CeA). Peripheral actions of GCs and insulin redistribute energy stores to central fat; a signal from abdominal fat stores serves to inhibit CRF activity in the paraventricular hypothalamus (PVN).
the meso-limbic dopaminergic brain “reward” system. Adrenalectomy decreases dopamine release specifically in the shell of the nucleus Accumbens (n. Accsh) in response to both drug injections and hypothalamic self-stimulation, and treatment with corticosterone restores both to normal (Barr et al., 2000; Goeders, 2002). Moreover dopamine transporters in the n. Accsh are reduced by adrenalectomy and restored in a dose-related fashion by corticosterone treatment (Sarnyai et al., 1998). Thus, responsivity to many stimuli is altered by the GC milieu apparently acting on the dopaminergic system in n. Accsh. Taken together, these results suggest strongly that corticosterone may generally increase food-associated ‘drives,’ stimulus salience or motivation, possibly through augmented dopamine secretion in the n. Accsh.

But, corticosterone does not appear to increase feeding-motivated behaviors under all conditions. Although adrenalectomized rats eat slightly less chow than controls, and corticosterone restores chow intake to normal, there is not a corticosterone dose-related increase of chow intake in adrenalectomized rats. The drive to obtain food is one of the most potent that we have, and this observation appeared to negate the drive-promoting effect that we attempted to ascribe to corticosterone. However, when rats are made diabetic with streptozotocin (that kills pancreatic B-cells, and thus insulin secretion), a marked, dose-dependent effect of corticosterone on intake of rat chow is revealed. A major difference between adrenalectomized and adrenalectomized-diabetic rats is the lack of insulin; moreover, circulating insulin concentrations increase directly as a function of circulating corticosterone concentrations in adrenalectomized rats (Dallman et al., 2002).

In a recent series of experiments, we have restated the effects of increasing corticosterone on chow intake and tested in similar experiments the effects of increasing steroid on lard ingestion in adrenalectomized rats (la Fleur et al., 2004). The results of these experiments provide a possible explanation for the nonlinear effects of corticosterone on chow intake. As previously, increasing corticosterone concentrations increased insulin in adrenalectomized rats, and did not increase chow intake; however, chow intake was increased in a corticosterone dose-dependent fashion in adrenalectomized-diabetic rats. By contrast, increasing corticosterone concentrations did increase lard intake in a dose-related fashion in adrenalectomized rats but did not affect lard intake in adrenalectomized-diabetic rats. Finally, when adrenalectomized-diabetic rats treated with high corticosterone were also infused subcutaneously with low doses of insulin, lard intake was directly proportional to circulating insulin concentrations in the diabetic rats (la Fleur et al., 2004). The results of these experiments suggest strongly that corticosterone is, indeed, a hormone that generally increases food-associated drives or motivation; it may be that insulin determines the preference for which foods are ingested.

1.3. Chronic stress recruits CRF systems in brain (Fig. 1, bottom right middle), but stress and GCs also increase the relative intake of “comfort foods” that damp stress responses

Chronically stressed rats persistently hypersecrete glucocorticoids during application of the stressor, compared to unstressed controls. Characteristically, if subjected to a new stressor during a period of chronic stress, hypothalamic CRF, ACTH, and corticosterone responses are increased, compared to control, as are autonomic and behavioral responses (Dallman et al., 2002). These responses are probably a consequence of recruitment of a central stress response network (Dallman et al., 2002) regulated by increased activity in the central, non-hypothalamic CRF system (Schulkin et al., 1994), and induced by an action of corticosterone at the amygdala (Shepard et al., 2000). Thus, during chronic stress, corticosterone acts in a feed-forward, positive fashion to augment acute ACTH secretion while still limiting its duration through the rapid negative feedback effect. When the actual stress episode is over, systemic activity in the HPA axis (ACTH and GCs) may be remarkably subnormal, as is seen in patients with post-traumatic stress disorders (Aardal-Eriksson et al., 2001) and in rats after withdrawal from morphine (Houshyar et al., 2004).

Because it seems clear that in the presence of insulin elevated glucocorticoids increase drive for pleasurable foods, we tested whether exposing intact rats to repeated restraint stress altered the amount of “comfort foods” they ingested (Pecoraro et al., 2004). Rats were provided with dishes of lard and bottles of 30% sucrose as well as chow for three day to remove any neophobia for these foods before they were exposed to restraint. After a day without these “comfort foods,” in a 2 × 2 design, half of the rats were resupplied with ad lib access to “comfort foods” and half were exposed to 3 h/day tube restraint stress for five consecutive days.

Because of the prior ingestion of “comfort foods” the two groups eating these were fatter. Generally, adult male rats reduce chow intake and stop growing during periods of sustained or repeated stress (Dallman and Bhatnagar, 2001); eating “comfort foods” during repeated restraint allowed this group both ponderal growth and increased caloric efficiency during chronic stress. The increased caloric efficiency (g gained/cal ingested) suggests that the normal degree of stress-induced sympathetic neural outflow was reduced in the stressed group eating “comfort foods.” Rats that ate “comfort foods” had reduced HPA responses to restraint and lower basal CRF in the hypothalamus (Pecoraro et al., 2004).
In another set of experiments, we held corticosterone constant at normal and stress concentrations after adrenalectomy, and exposed half of the rats to cold stress ±30% sucrose to drink (Bell et al., 2002). Again, “comfort food” reduced the degree of metabolic stress induced by cold, suggesting strongly that “comfort food” reduces the degree of stressor-induced sympathetic responses.

In both of the above experiments, provision of “comfort foods” reduced the magnitude of HPA responses to the stressors (Bell et al., 2002; Pecoraro et al., 2004). Similar inhibition of the HPA axis occurs when a variable stress paradigm is applied to obesity-sensitive, but not obesity-resistant rats eating a high-fat diet (Levin et al., 2000). Thus, it appears that provision of “comfort foods” either as fat, high sucrose concentrations, or the combination reduces both autonomic and HPA responses to repeated stressors in rats.

There is some evidence that “comfort foods” given to chronically stressed rats may negate chronic stress-induced inhibition of dopamine release that occurs in the n. Acc sh. Although acute stress stimulates dopamine secretion in both n. Acc sh and prefrontal cortex (Berridge, 2004), chronic stress inhibits dopamine secretion in these sites (see (Nanni et al., 2003)). A learned appetitive behavior in combination with chronic stress prevented the inhibitory effects of a chronic stress procedure on dopamine output and dopamine transporter density in n. Acc sh (Nanni et al., 2003). Moreover, brief scheduled presentation of palatable sucrose increases chow intake, and dopamine transporters in the ventral tegmental area and n. Acc sh of rats on a restricted, but not ad lib chow diet (Bello et al., 2003). Restricted feeding alters HPA activity so that it is maximal just prior to expected caloric intake (Pecoraro et al., 2002). Thus, it may be that the inhibition of HPA responses to stressors in rats eating “comfort foods” is explained by the interplay between the negative effects of chronic stressors, and the positive effects of “comfort foods” on inputs to the VTA-n. Acc sh reward network.

1.4. But GCs also act on peripheral energy storage organs to promote central obesity (Fig. 1, bottom right)

In the presence of insulin, passive treatment of rats with high GCs reduces chow intake, body weight, sympathetic activity but increases fat stores (Dallman et al., 2002; la Fleur et al., 2004). With chronic stressors and endogenous corticosterone, there is also decreased chow intake, body weight and a relative increase in central fat (Houshyar et al., 2004). This is a result of the action of GCs in mobilizing small molecules (amino acids and fatty acids) from peripheral protein (muscle, skin) and fat stores for use in hepatic gluconeogenesis and ketogenesis. In the presence of insulin and high GCs, fat accrues in intra-abdominal stores, where lipids serve, upon mobilization, as immediate further substrate for hepatic gluconeogenesis as well as ketones for direct energy use by brain (Peters et al., 2004).

Intra-abdominal fat stores appear to serve as an excellent surrogate for an indirect metabolic negative feedback signal of glucocorticoids since they are highly negatively correlated with hypothalamic CRF expression and HPA responsivity in both adrenalectomized-corticosterone replaced, and in intact, chronically stressed rats (Dallman et al., 2003; Houshyar et al., 2004). The specific signal to brain that represents increased abdominal fat stores is still unidentified. However, it seems clear that this signal does act at brain to reduce the adverse effects of a recruited chronic stress response network, and probably makes animals (and people) feel better under conditions of chronic stress.

1.5. Summary (Fig. 1) and perspective

Central CRF networks are recruited by chronic stressors and elevated GCs initiating recruitment of central CRF activity in the amygdala. Increased central activity of the CRF network stimulates all monoaminergic cell groups, as well as premotor autonomic and other limbic structures resulting in the typical arousal, behavioral changes, autonomic, and neuroendocrine changes that accompany the chronic imposition of a stressor. By contrast, elevated GCs appear, through a variety of means, to counteract the effects of central CRF, which they have initiated. Together with insulin, the GCs stimulate drive for and ingestion of “comfort foods” that may directly result in reduction of the negative effects of the chronic stressor in the n. Acc sh through stimulation of the anterior, more pleasure-associated part of this cell group, thus reducing the weight of the stress-stimulated posterior, more defensive part (Berridge, 2004). Furthermore, the shift in caloric intake from chow to preference for “comfort foods,” together with elevated GCs and insulin, reorganize energy stores from a peripheral to a central distribution, primarily as abdominal fat. A signal associated with this fat depot appears, as with eating “comfort foods” to reduce the influence of the chronic stress network on behaviors, autonomic, and neuroendocrine outflow.

There is evidence that this sequence of events of chronic stressors on rats also may apply to humans. Students under stress report shifting ingestion from normal (fruits, vegetables, fish, and meat) to sweet and savory foods (Oliver and Wardle, 1999). Moreover, stress precipitates binge eating (Freeman and Gil, 2004; Schoemaker et al., 2002), and women under acute lab stress increase “comfort food” intake (Epel et al., 2001). Unfortunately, persisting in this behavior either as habit or for self-medication yields abdominal obesity. Increased abdominal fat stores are strongly associated with the metabolic syndrome, hypertension, type 2
diabetes, and cardiovascular disease, morbidity and mortality (Friedman, 2003; Stunkard et al., 2003).

Rather than indulging in “comfort foods” to feel better during periods of chronic stress, it behooves us to find a means to remove or reduce the chronic stressor. A recent evaluation of the effects of a program designed to remove impoverished people from inner city public housing where the poverty level was initially >40% to sites with far less poverty showed significant self-reported effects that included both reduced sensations of stress, increased peacefulness, and weight loss, as compared with a randomly assigned control group who remained in high-poverty areas (Orr et al., 2003). Perhaps it would help to relieve some of the current epidemic of obesity were policy-makers aware of the insidious effects of not actively seeking to relieve sources of uncontrollable chronic stressors in our current lives.

References


