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Self-medication with sucrose

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Abstract

For many individuals, stress promotes the consumption of sweet, high-sugar foods relative to healthier alternatives. Daily life stressors stimulate the overeating of highly-palatable foods through multiple mechanisms, including altered glucocorticoid, relaxin-3, ghrelin and serotonin signaling in brain. In turn, a history of consuming high-sugar foods attenuates the psychological (anxiety and depressed mood) and physiological (HPA axis) effects of stress. Together the metabolic and hedonic properties of sucrose contribute to its stress relief, possibly via actions in both the periphery (e.g., glucocorticoid receptor signaling in adipose tissue) and in the brain (e.g., plasticity in brain reward regions). Emerging work continues to reveal the bidirectional mechanisms that underlie the use of high-sugar foods as ‘self-medication’ for stress relief.

Introduction

Stress is typically defined as a real or perceived threat to homeostasis or well-being, and can be either physical (e.g., illness, injury) or psychological (e.g., financial insecurity, overscheduled time demands, troubled interpersonal relationships) in nature (reviewed in [1,2]). Stress has clear effects on mood and behavior, including increased anxiety and/or depressed mood. In addition, stress-regulatory brain circuits are activated during stress and orchestrate physiological responses that minimize homeostatic disruption and promote survival. Activation of pre-autonomic brain regions rapidly increases sympathetic nervous system (SNS) tone. This ‘fight or flight’ response acts to mobilize and distribute stored energy. In addition, hypophysiotropic neurons in the paraventricular nucleus of the hypothalamus (PVN) are activated during stress, resulting in the stimulation of the hypothalamic-pituitary-adrenocortical (HPA) axis. More specifically, activated PVN neurons release corticotropin releasing hormone (CRH) and other releasing hormones into the portal circulation, which then act on the anterior pituitary to evoke the secretion of adrenocorticotropin hormone (ACTH) into systemic circulation. ACTH stimulates the production and release of glucocorticoid hormones (e.g., cortisol in people and corticosterone in rodents) from the adrenal cortex. Circulating glucocorticoids then act on

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receptors (glucocorticoid receptor (GR) and mineralocorticoid receptor (MR)) throughout brain and body to promote and sustain the mobilization of stored energy, while also limiting further HPA axis activation via negative feedback in brain and pituitary. In this manner, coordinated activation of the SNS and HPA axis during an acute stress helps to maintain homeostasis and promote survival.

Excessive, repeated or chronic activation of the HPA axis and SNS has a number of negative consequences. For instance, excessive glucocorticoid exposure is associated with cognitive decline and diminished bone density, while persistent elevations in SNS drive are linked with cardiovascular dysfunction (reviewed in [2]). This implies that the magnitude of HPA axis and SNS responses should be ‘tuned’ to the particular needs of the individual. In addition, mounting evidence suggests that an individual's metabolic status and diet are important factors that impact the magnitude of physiological stress responses (reviewed in [2]). As a consequence, individuals may develop dietary and metabolic strategies to curb excessive activation of these stress systems. For example, people may increase their consumption of tasty, highly-palatable foods during stress because these so-called ‘comfort’ foods blunt the psychological and physiological impact of stress [3]. This review summarizes recent research centered on the idea that some individuals eat tasty, sugar-laden foods as ‘self-medication’ for stress.

Stress alters feeding behavior

The impact of stress on overall food intake varies considerably between individuals, with ~ 35-70% of people reporting increased, and ~ 25-40% reporting decreased, total caloric intake during stress [4-7]. Several factors have been identified that likely contribute to this variability in stress effects, such as the type and intensity of the stressor, as well as the individual's prior experience with food. Imminent, intense, direct physical threats are linked primarily with reduced food intake in both people [8,9] and rodents [10-12], whereas more mild “daily life” and social stressors may predispose for overeating in people [13-17], non-human primates [18] and rodents [19]. Moreover, a history or prior food restriction and being a ‘restrained’ or ‘emotional’ eater increases risk for stress-induced overeating in humans [5,16,17] and rodents [20].

In addition to impacting total food intake, stress also affects the types of food that are eaten. Stress generally promotes the consumption of highly-palatable, calorically-dense foods relative to less tasty, more nutritious foods [5,13,14,21-26], even among people who decrease their total caloric intake [5]. This is particularly true for high-sugar foods, with ~ 60-70% of people reporting that they eat more sweet foods like candy, chocolate, cakes and cookies during times of high stress [5,7,25]. Likewise, the consumption of cake, chocolate and/or cookies approximately doubles during a laboratory-induced stressor [7], particularly for emotional eaters [22]. Consistent with this idea, chronic stress exposure to rodents typically reduces intake of their normal, nutritionally-balanced chow [10,27-29]. However, when highly-palatable foods like sucrose drink are also freely available, the intake of sucrose is preserved during stress [10,27-29], resulting in a greater proportion of daily calories from sugar. Furthermore, the anorectic effects of stress on chow intake is prevented

in rats with a history of intermittent, but not continuous, access to sucrose, thus maintaining overall caloric intake during stress [29].

The mechanisms by which stress promotes the intake of sweet foods are not clear, but likely involve increasing the motivation or ‘wanting’ of these highly-palatable foods. Stress increases activation of brain reward-related structures by palatable foods [21,30], and people report that induction of a depressed, stress-like mood increases cravings for chocolate [31]. Moreover, both people and rats are willing to do more work to obtain sucrose, chocolate and other desserts during stress [31-33]. Notably, this increased motivation for high sugar foods can occur despite stress-induced anhedonia, in which the ‘liking’ of mildly sweet foods (such as dilute saccharin or sucrose drink) is reduced [10,11,34,35]. Stress-evoked glucocorticoids likely contribute to the increased motivation to eat during stress; glucocorticoids can act in brain to increase total food intake, as well as preference for sweet foods and other carbohydrates [36-40]. Recent evidence indicates that brain relaxin-3 also promotes sucrose intake following stress. Stress can increase the mRNA expression of relaxin-3 and its receptor in brain [41-43], and relaxin-3 signaling can enhance food intake, including the consumption of high-sugar foods [44-46]. Moreover, pharmacological antagonism of relaxin-3 receptor signaling in brain prevents stress-induced increases in sucrose consumption in binge-like eating prone rats (i.e., the subset of female rats that escalate their intermittent sucrose intake when given repeated footshock stress) [42]. Endocannabinoid signaling may also stimulate stress-eating, as loss of cannabinoid receptor 1 on serotonergic neurons blunts the increased sucrose preference that occurs following chronic social defeat stress in mice [47]. Lastly, the gut hormone ghrelin is induced by stress and may act in brain to promote palatable food intake during stress (reviewed in [48]).

It should also be noted that while many people increase sweet food intake during stress, not all do. Recent work suggests that some of these individual differences in stress-eating are related to genetic differences in serotonin neurotransmission. Following a laboratory stressor, people generally choose to eat sweet high-fat snacks more than savory high-fat snacks; however, this stress-induced preference for sweet fatty foods occurs primarily for people who are homozygous for a short-allele (S/S; as opposed to the long-allele, L/L) polymorphism in the serotonin transporter gene [49]. Likewise, while both S/S and L/L subjects report greater appetite for sweet snacks following an academic exam stress, this occurs to a larger extent for the S/S subjects [50]. Collectively, this suggests that altered serotonin signaling may predispose for overeating high-sugar foods in response to stress. Consumption of these sweet foods may then act to confer both psychological and physiological stress relief, as described below.

Stress relief by dietary sucrose

When people who overeat tasty foods during stress are asked why they do so, 53% reply that the primary reason is because these foods make them feel better (i.e., more relaxed or comforted) [7]. Consistent with this idea, people often experience greater happiness, improved mood, and less perceived stress after eating sweet foods [51-53]. These psychological improvements are also accompanied by an attenuate HPA axis response to stress [54-56], particularly for stress-prone subjects [57]. Moreover, when rodents are given

the option to eat highly-palatable foods like sucrose, their responses to stress are similarly blunted – these effects include both reduced HPA axis tone and diminished behavioral anxiety [10,27,29,58-64], indicating a capacity for both psychological and physiological stress relief.

Recent research has focused on understanding how high-sugar foods reduce stress, and has revealed that there are likely multiple mechanisms underlying these effects. Much of this work was borne from the initial observation that unlimited consumption of 30% sucrose drink, but not the artificial sweetener saccharin, normalizes the elevated CRH mRNA expression in the PVN that otherwise occurs following adrenalectomy (due to the loss of glucocorticoid negative feedback) [65]. These results indicate that HPA axis activity can be profoundly inhibited by the metabolic properties of sucrose (e.g., macronutrients, calories). Consistent with this idea, when adrenal-intact rats are given free access to 30% sucrose drink, they derive large portions of their daily calories from sucrose and have blunted HPA axis responses [59,61,64,66]. Furthermore, the expression of CRH mRNA is inversely related to the size of the mesenteric fat depot in sucrose-fed, adrenalectomized rats, leading to speculation that the visceral fat itself may limit the HPA axis through an unknown means [3,67]. New research now provides some evidence to support this possibility. Transgenic mice with reduced GR expression in adipose tissue have increased CRH mRNA expression in the PVN, as well as an elevated plasma corticosterone response to stress, indicating that GR-signaling in adipose tissue can exert an inhibitory influence on central HPA axis tone [68]. Although it is not yet clear whether this type of GR–adipose signal contributes to HPA inhibition by dietary sucrose.

Importantly, at least some of the stress-relieving properties of sucrose appear to depend on its pleasurable and rewarding properties, particularly when it is offered in limited amounts. When rats with free access to chow and water are given additional access to a small amount (4 ml) of 30% sucrose drink twice daily for 2 weeks, both anxiety-related behaviors and the HPA axis response to restraint stress are attenuated relative to water-controls [10,58]. This limited sucrose intake (LSI) paradigm does not alter total body weight nor percent body weight since rats reduce their chow intake slightly to compensate for the calories provided by the sucrose drink (~9 calories/day, or ~10% of total daily caloric intake) [10,58]. When the artificial sweetener saccharin (0.1%) is offered in this same paradigm, it reduces the HPA axis response similar to sucrose, and when the sucrose drink is instead administered by twice-daily gavage it no longer attenuates the HPA response to restraint [58]. Furthermore, when male rats are given limited intermittent access to another type of naturally rewarding behavior (sexual activity) the HPA axis response to stress is also diminished [58]. Collectively these results suggest that the blunted HPA reactivity that occurs following LSI does not depend upon the macronutrient and/or caloric properties of sucrose, but rather is primarily mediated by its hedonic and/or rewarding properties.

Consistent with this idea, neuronal activity in brain reward pathway appears to be critical for LSI stress relief. Sucrose intake activates several reward-regulatory brain sites, and over the long-term induces synaptic plasticity in these regions [58,69-71]. LSI also attenuates stress-induced cFos mRNA induction in the basolateral amygdala (BLA) – a brain region that is important for both reward and stress regulation [10]. Neuronal activity in the BLA is

required for LSI stress relief since excitotoxic lesion of the BLA prior to LSI prevents the blunted HPA reactivity despite equivalent sucrose intake [58]. Finally, in order to more broadly identify the neuronal network by which LSI blunts HPA axis activity, statistical modeling was performed on a large dataset that measured multiple synaptic plasticity proteins in several reward- and stress-regulatory brain sites following LSI. The results implicated two concurrent neuronal pathways underlying the stress relief – reduced activity of a stress-excitatory pathway between the BLA and medial amygdala, as well as potentiation of a stress-inhibitory pathway from the bed nucleus of the stria terminalis, which together result in less stress-excitatory drive to downstream effector sites like the PVN [69]. Future work can now empirically test these predictions to uncover the neuronal mechanisms by which the hedonic and rewarding properties of sucrose contribute to its stress-relieving effects. Further work will also be needed to determine whether the mechanisms of stress relief vary across particular conditions. For example, reward-based mechanisms likely predominate when the amount of sucrose consumed is relatively small, whereas the metabolism-based mechanisms may play a more prominent role as sucrose intake escalates.

Summary and perspectives

Stress causes many individuals to increase their consumption of sweet, high-sugar foods, in part because these foods provide stress relief. However, over the long term this coping strategy can promote obesity and metabolic dysfunction. Furthermore, the repeated consumption of high-sugar foods during stress may develop into a habit, and stress further engrains habitual behaviors [72] – making it increasingly difficult to stop the pattern of stress-eating. Additional insight into the mechanisms underlying sucrose ‘self-medication’ is needed, particularly since modern life combines easy access to high-sugar foods with highly-stressful lives.

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Highlights

- For many individuals, stress promotes the consumption of sweet, high-sugar foods
- Mediators of stress-eating include altered glucocorticoid and serotonin signaling
- Sweet foods can also reduce the psychological and physiological impact of stress
- Stress responses are blunted by both the metabolic and hedonic properties of sugar
- This suggests that some people overeat high-sugar foods to relieve stress

Figure 1.

Stress promotes the choice of sweet, high-sugar foods relative to less-tasty alternatives for many individuals, particularly when typical daily-life stressors (like work, school, and interpersonal relationships) are experienced. Stress likely stimulates the overeating of highly-palatable foods through multiple mechanisms, including altered glucocorticoid, relaxin-3, ghrelin and serotonin signaling in brain. In turn, a history of consuming high-sugar foods attenuates the physiological (e.g., HPA axis activation) and psychological (e.g., anxiety, negative mood) impact of stress. Both the metabolic and hedonic properties of sucrose contribute to its stress relief via a combination of effects in the periphery (e.g., GR-signaling in adipose tissue) and brain (e.g., plasticity in brain reward regions). Future work will undoubtedly reveal additional mechanistic insights into the bidirectional relationship between stress and high-sugar foods.