Review

Stress-induced obesity and the emotional nervous system

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Stress and emotional brain networks foster eating behaviors that can lead to obesity. The neural networks underlying the complex interactions among stressors, body, brain and food intake are now better understood. Stressors, by activating a neural stress–response network, bias cognition toward increased emotional activity and degraded executive function. This causes formed habits to be used rather than a cognitive appraisal of responses. Stress also induces secretion of glucocorticoids, which increases motivation for food, and insulin, which promotes food intake and obesity. Pleasurable feeding then reduces activity in the stress–response network, reinforcing the feeding habit. These effects of stressors emphasize the importance of teaching mental reappraisal techniques to restore responses from habitual to thoughtful, thus battling stress-induced obesity.

Introduction

We find ourselves in the middle of a severe epidemic of obesity that affects not only adults but also has recently permeated younger generations [1–6]. An understanding of the underlying physiological causes of this growing problem is required for its solution.

The physiology of feeding behavior has been studied for many years, generally providing rodents or other experimental animals with standard lab chow. These studies, using a single bland food, perforce concentrated on the hypothalamic and brainstem regulation of energy balance. The emergence of leptin as a key fat hormone that stimulates secretion of the anorexigenic and sympathetic–stimulatory neuropeptides and inhibits secretion of the orexigenic and parasympathetic–stimulatory neuropeptides was of critical importance in understanding homeostatic regulation of energy balance [1,7–10]. Moreover, findings about other hormonal signals that acutely affect feeding, such as ghrelin and other gut peptides activated by fasting or feeding, added to our knowledge about regulators of energy balance [9,10]. However, it has become glaringly obvious that voluntary behaviors, stimulated by external or internal challenges or pleasurable feelings, memories and habits can override the basic homeostatic controls of energy balance [11–17].

The increased amount of perceived stress experienced by individuals in modern society affects feeding behavior [18–20]. In fact, a recent study showed that sadness favored eating of high fat/sweet, hedonically rewarding foods, whereas intake during a happy state favored dried fruit [21]. The basis for this behavior and others that lead to obesity are slowly becoming understood. They include cortical and subcortical pathways that involve learning and memory of reward and pleasure, as well as habit formation and decreased cognitive control. Elevated stress hormones and palatable food intake and the consequent accretion of fat can serve as feedback signals that reduce perceived stress [22], thus reinforcing stress-induced feeding behavior.

This review focuses on emotional and regulatory brain networks and how stress and glucocorticoid (GC) secretion foster behaviors that can lead to obesity. From large numbers of recently available structural and functional magnetic resonance imaging (MRI, fMRI) studies on people, and the relationships between stress and feeding found in selected animal studies, the role of stress on the brain and resulting behaviors is becoming rationalized. Together, these studies suggest that programs promoting learned increases in use of the executive brain during periods of stress can reduce stress-induced eating and resultant obesity.

Stress and food intake

People usually change their eating behaviors when they perceive themselves to be stressed or are under persistent external interpersonal, financial or other strains. Although approximately 20% of people do not change feeding behaviors during stressful periods, the majority do; around 40% or more increase and 40% or less decrease caloric intake when stressed [14,23–25]. In prospective studies, it appears that those who initially are at the upper range of normal, or are overweight, are generally more inclined to increase weight when stressed, whereas those who are of normal- or underweight do not [2,24,26]. It seems possible that the difference between the gainers and the losers might be a consequence of higher insulin concentrations in people with higher body mass index.

In both people and animals, a shift toward choosing more pleasurable or palatable calories occurs whether or not total caloric intake increases with stress [14,19,22,27–29]. With choice [30,31], the foods eaten during times of stress typically favor those with increased fat and/or sugar content (Figure 1). Under controlled lab circumstances, acute physical or emotional distress induces increased intake of 'comfort' foods in humans and animals [21,29–34], even when they are not hungry and have no homeostatic need for calories [31,35].

Stress-induced feeding is also observed in normal weight women who consciously monitor their food intake

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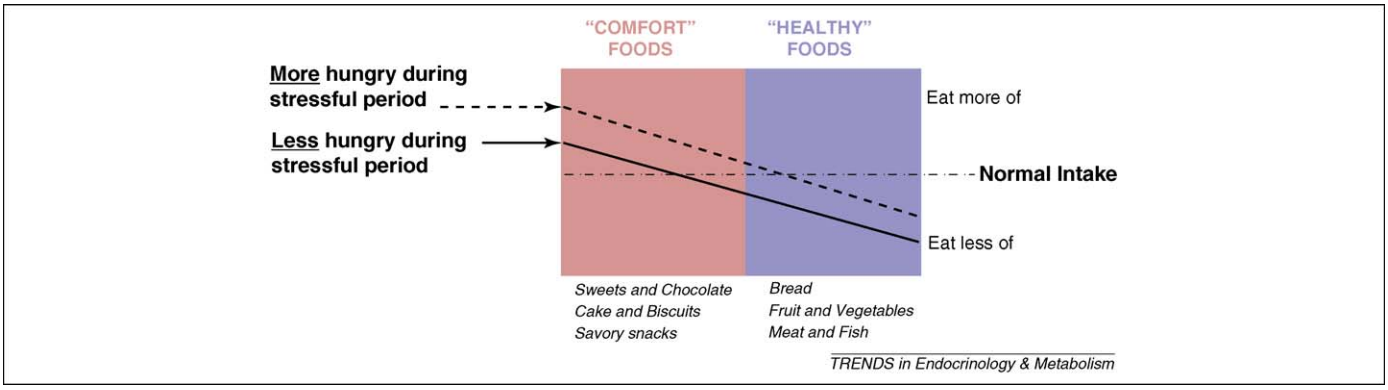

Figure 1. During stressful periods, there is a change in what type of food is eaten, independent of hyperphagia or hypophagia. There is a shift in food intake toward 'comfort foods' that is independent of whether total caloric intake increases (dashed line) or decreases (unbroken line) from normal intake (horizontal dot–dashed line). Student intake was retrospectively interrogated during periods of no stress (normal) or exam stress; the type of foods eaten and the amounts of foods were compared during the two periods. Whether or not food intake increased or decreased, the type of food ingested shifted toward the more palatable sorts. Reproduced, with permission, from Ref. [14].

to remain slim exhibiting 'dietary restraint' (although this can reflect 'emotional' eating [14]) [36,37]; such restraint might, through the mental effort it takes, itself serve as a chronic stressor [38]. Stress-induced feeding in women who practice dietary restraint can represent an ironic example that is observed when mental control is challenged by increased mental load [39]. Disinhibition of dietary restraint or possibly emotional eating is likely to occur after a stressor or in the presence of palatable foods in a social setting [37,38]. It has also been suggested that stress-induced eating is similar to the effects of stress on relapse to drug addiction [40,41]; indeed, the same brain networks that include both initial liking and learned motivation regulate these behaviors [42,43].

The emotional nervous system

Studies using imaging techniques in humans have become invaluable in shedding light on the integration of emotion into behavior. Experimental animals cannot be asked how something feels except through their behaviors, and those behaviors might not be correctly interpreted or elicited in inappropriate contexts. Integration of emotion into ongoing behavior is essential to provide the motivation to perform the behaviors. This is shown by many neuroscience studies on animals, in which essentials (food and drink) are rationed, and then supplied as rewards that induce the animals to perform desired tasks.

In the past decade, it has become increasingly clear that the integrated activity of brain networks, rather than single sites, determines coherent and integrated behavioral (muscular), autonomic and endocrine responses to what is happening at that moment. Moreover, it is certain that 'what's going on', both outside and inside the body, perceived by the primary senses (vision, audition, touch, taste, smell) and by interoceptors (stretch, pain, temperature, metabolites and hormones) determines the basis for how one feels and the various responses that might result.

A simple sketch of the anatomical parts of brain involved in stress and feeding behavior, based on imaging studies (Figure 2) shows that the entire brain is involved. Although complex, this figure represents only some of the components in the networks of interactions between stress and obesity. At the cortical level, the emotional brain is embedded in the anterior insula that provides 'feelings' resulting from integration of exteroceptive and interoceptive inputs [44] and 'motivated behavior' resulting from integrated output from the anterior cingulate cortex [45–48]. It is proposed that an instantaneous replica of the momentary integrated information coming from inside and outside the body is copied into the anterior insula and gives rise to conscious feelings [46,48]. The anterior insula and anterior cingulate communicate rapidly in large brained mammals (whales, humans, elephants, great apes) through specialized neurons, and the anterior cingulate serves as the consciously motivated output in response to stimuli, based on how the 'self' feels [46,49,50]. It is very important to understand that at each organizational level (spinal, medullary, pontine, midbrain, limbic and thalamocortical), there is communication between the sensory inputs and motor outputs. Moreover, there is also vertical, reciprocal communication from the cortex to each of the lower levels of brain. Thus, cognitive components of the emotional nervous system can alter ongoing activity at each of the subcortical components.

The components essential for homeostatic regulation of energy balance are shown in Figure 2. Neurons in the hypothalamus, brainstem and afferent nerves are well studded with leptin, insulin and other hormonal receptors [51–53]. These subcortical sites are sufficient to regulate adequate food intake to sustain energy stores [54–56]. However, components in the limbic brain and frontal cortex (Figure 2) can override the basic maintenance of energy balance and result in either an underweight or overweight phenotype [13].

Positron emission tomography studies and fMRI analysis found that the amygdalae specifically respond to both positive and negative alerting stimuli in humans [57]. The nuclei accumbens, innervated by dopaminergic neurons from the ventral tegmental area in the brainstem, provide motivation to accomplish a behavior, either at the automatic, habitual level, through the basal ganglia [58], or consciously and with forethought, through the prefrontal cortex [12,13,59]. When a verbal instruction about how to deal with emotion-provoking stimuli (reappraise) is given to subjects before the stimuli, the prefrontal response increases and the amygdalar response decreases and can be entirely inhibited [57,60,61]. Such verbal instruction, or chemical manipulations of the prefrontal cortex in rodents,

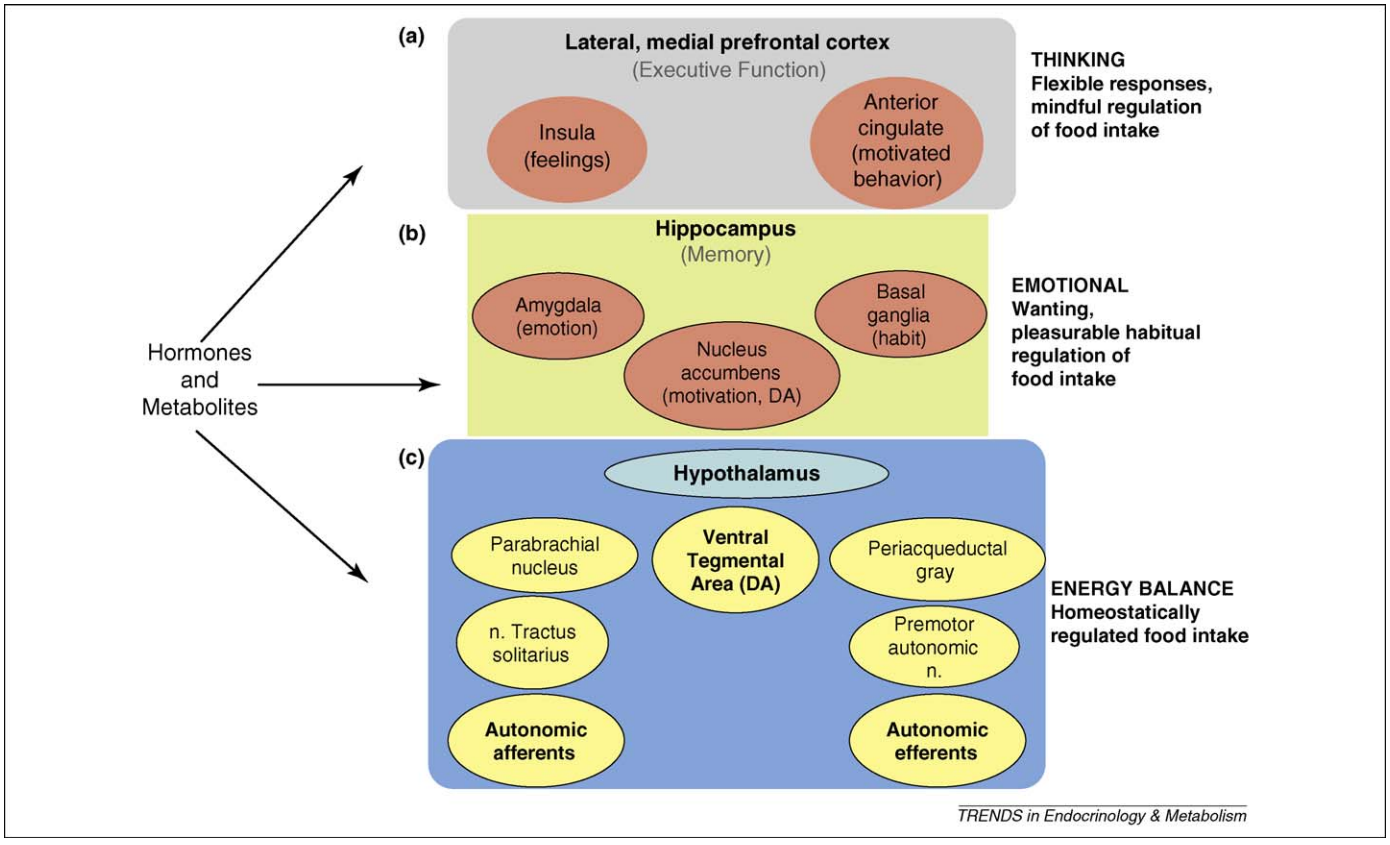

Figure 2. Brain structures engaged in feeding behaviors. **(a)** At the cortical level, the emotional brain is embedded in the anterior insula that provides 'feelings' and in the anterior cingulate cortex that governs 'motivated behavior'. **(b)** The limbic brain is responsible for emotional (amygdala), motivational (nucleus accumbens) and habitual (basal ganglia) responses, whereas **(c)** the brainstem, containing the hypothalamus, brainstem and spinal cord, regulates energy balance. Afferent inputs to the brain and to emotional and cortical structures are shown on the left, and efferent outputs from cortical and subcortical habitual and emotional structures are shown on the right. Horizontal interactions between afferent and efferent components exist at each level, and structures are also bidirectionally connected vertically. Although the hypothalamic neurons are sufficient to regulate energy intake, components in the limbic brain and frontal cortex can override the basic maintenance of energy balance and result in either an underweight or overweight phenotype. The cell groups shown in yellow represent the brainstem and spinal cord portion of the brain that is engaged with the homeostatic maintenance of energy balance. The cell groups shown in orange can cause either an increase or decrease in food intake. DA, drug addiction.

activates the infralimbic prefrontal cortex, which features prominently in extinction behavior, and can inhibit amygdalar and accumbal as well as adrenocortical activity [62–64]. This highly complex region is where cognitive control of feelings and motivation is regulated [65,66]; it is activated in individuals with restriction eating disorders (Box 1) who are shown pictures of palatable foods [67]. Simplistically, at the unconscious level, the amygdalae are the sites at which emotions arise and the nuclei accumbens provide motivation to carry out habitual behaviors appropriate to those emotions, whereas the cognitive, executive control of emotions and drive is heavily regulated by prefrontal cortical structures [68].

Box 1. Restriction eating disorders

Restriction eating disorders are reviewed in Refs [100–103]. Anorexia nervosa (AN) is excessive and habitual regulation of restricted food intake, whereas bulimia nervosa is restricted food intake with frequent loss of control and binge eating followed by purging [104]. Many people who do not meet criteria for an eating disorder do restrict their food intake with the goal of weight stability, and some of these restricted individuals eat more than they feel they should during disinhibition of restriction. There is some disagreement about what tests best detect restricted eaters and restricted eaters with disinhibition [105]. However, restricted eaters, such as patients with AN, appear to engage the prefrontal cortex when shown highly palatable foods, whereas disinhibited restrictors engage more amygdalar activity [106].

Stress, glucocorticoids, corticotropin-releasing factor and the emotional nervous system

Threatening and cognitively meaningful stimuli activate the emotional nervous system in humans and lab animals [22,69]; the emotional brain and other prefrontal cortical outputs determine to a large extent what behavioral output (e.g. fight, flight or freezing) will be chosen [22]. Stress-induced elevations in GC secretion appear to intensify emotions and motivation [69,70]. An overview of the effects of elevating GC on a variety of rat behaviors drawn from different studies strongly suggests that this stress hormone increases wanting or motivation. It is clear that context and training, as well as conditions for testing the animal [71], are essential for a given effect; however, in all cases, increasing GC increases the amplitude of the behavioral effect, perhaps through actions at the ventral basal ganglia in rats, and possibly in humans [72].

Stressors that provoke hypothalamo-pituitary-adrenal (HPA) GC secretion also recruit a central stress–response system, mediated by corticotrophic releasing factor (CRF) neurons in the amygdala, that appears to bias normal responses toward net increased output of activity from the limbic brain that contains the amygdala and nucleus

accumbens ([73], Figure 2). Elevated GC is required to stimulate CRF synthesis and secretion from the central nucleus of the amygdala and other limbic sites, and axons from these CRF neurons innervate much of the limbic and cortical brain, where CRF receptors are found. They also innervate and affect activity in the brainstem monoaminergic (noradrenergic, serotoninergic and dopaminergic) neurons, which are responsible for alerting not only the brain to cause discriminative and motivated behaviors but also the hindbrain and premotor autonomic neurons [69,74,75]. GCs additionally act on the monoaminergic neurons to increase their amine synthesis and secretion [69,75]. The resulting activation of this limbic stress–response network ensures that the HPA response to renewed stressors remains normal or facilitated, and overrides GC-induced inhibition of CRF synthesis and secretion in the hypothalamic motor neurons of the HPA axis. This could explain the apparent insensitivity to exogenous dexamethasone or other steroid feedback tests in chronically stressed individuals (see Refs [69,74,75]) and certainly prepares the stressed organism to respond to future insults.

GC receptors are also heavily expressed in the executive brain of the prefrontal cortices, and chronic stressors activate norepinephrine secretion over these sites where GC implants inhibit stress responses (reviewed in Ref. [63]); the executive brain has the potential to control activity in limbic brain when it is engaged [65], although in stressed rodents, and perhaps man, executive dysfunction and prefrontal cortical remodeling occurs [76,77].

GC, food intake and insulin: 'comfort foods'

GC infusions increase caloric intake in both humans and rats [70,78]. Interestingly, with only chow available, adrenalectomized rats treated with various levels of corticosterone do not reliably eat more chow, but if sucrose and/or fat are available the rats increase intake of these foods in proportion to the circulating GC concentrations [70]. It is important to note that, as GCs increase, insulin secretion also increases, as is well-known from the strong association of Cushing's syndrome with type 2 diabetes [79]. In fact, when adrenalectomized rats become diabetic with streptozotocin, they increase chow intake in proportion to GC levels, but no longer increase sucrose intake above the amounts observed in the absence of steroid [70]. Thus, in the presence of pancreatic insulin, the combination of increasing GCs and insulin drive the intake of pleasurable fat/sugar, whereas, in the absence of insulin, increasing GCs drive intake of low fat/sugar, bland rat chow.

Treating corticosterone-injected, diabetic, adrenalectomized rats with insulin restores fat and/or sucrose intake and reduces chow feeding [80,81]. Thus, it appears that insulin plays a profound role in food selection, whereas GCs determine the motivation for selecting these foods, perhaps through their actions on dopamine secretion in the nucleus accumbens [82,83]. When insulin is injected into the brains of intact rats, it is clear that it acts both in the hypothalamus to decrease food intake, and at the ventral tegmental area to decrease dopaminergic activity and associated food intake behaviors [84]. These apparently discrepant sets of results can be resolved by the fact that our studies have moved rats from a condition of no insulin to low–normal concentrations, whereas injecting or infusing insulin into the cerebrospinal fluid must cause very high concentrations of insulin in the brain. Insulin-mediated actions are found throughout the brain and on afferent vagal nerves [85], and it appears that insulin has other effects than just on the hypothalamus and dopaminergic cell groups to determine what is eaten, with important sequelae for energy balance and stress responsiveness.

In the absence of corticosterone, insulin concentrations are low, food intake is reduced and rats contain lower fat stores than normal. However, adrenalectomized rats ingest ~30–40% of the amount of lard or sucrose eaten by intact rats. Remarkably, when available, additional calories from sucrose restore adrenalectomized rats to normal, not only in terms of fat stores but also in terms of hypothalamic CRF expression and expression of the rate-limiting enzyme for catecholamine synthesis in the upper brainstem (Table 1); this suggests that energy stores are critically important for normal activity in the central stress–response network [86]. Eating 'comfort foods' also alters stress responsiveness in intact rats. Under both acute and repeated restraint stress, CRF expression and ACTH secretion is reduced when rats are allowed to eat fat or sucrose in addition to chow [30,31,87]. Although increased ingestion of palatable foods during and after stressors might simply reflect a pleasurable activity that reduces the discomfort of stress, signals from eating these foods also reduce activity in the central stress–response network through reducing CRF hyperactivity. It appears probable that stress-induced activation of the emotional brain is reduced in animals and people with available palatable foods and plentiful energy stores [88].

GC, CRF, learning, memory and habit

Acting at least in the amygdala, hippocampus, insula, anterior cingulate and other areas of the prefrontal cortex (Figure 2), norepinephrine, GC and CRF are critical for learning and remembering, particularly following emotional events with negative valence [89–91]. Thus,

Table 1. Drinking 30% sucrose *ad libitum* has similar restorative effects to supplying replacement corticosterone in adrenalectomized rats compared with sham-adrenalectomized controls

	Adrenalectomy	Adrenalectomy + 30% sucrose	Adrenalectomy + corticosterone
In the CNS			
CRF in the CeA	Decreased	Normal	Normal
CRF in the PVN	Increased	Normal	Normal
DBH in the LC[a]	Decreased	Normal	Normal
In the periphery			
Insulin	Decreased	Normal	Normal
Fat depot weight	Decreased	Normal	Normal

[a]DBH=norepinephrine-synthesizing enzyme, dopamine B-hydroxylase, in the brainstem locus coeruleus; CeA = central nucleus of the amygdala; PVN = paraventricular nucleus of the hypothalamus.

when stress promotes GC-induced, insulin-delineated palatable food intake, memory is laid down for future recall of this coupling. An association is almost certainly made between 'feeling stressed' and 'feeling better' after indulging in 'comfort foods'. This can be a critical link between stressors and eating-induced obesity. Stressors promote more habitual behaviors at the expense of cognitive, goal-directed actions in humans [92,93]. Learned associations, when reinforced through synaptic plasticity, can turn into habits that are expressed through activity in the basal ganglia with little conscious recognition of the habit [58,94]. It is a small step to take, from cooling off emotional feelings induced by an intense, unmanageable stressor via eating rewarding foods, to instead using these foods to produce the same effect during lower intensity stimuli, such as ongoing low-grade stress, tiredness or repeated, small upsetting events.

The obvious problems with the habitual use of food to reduce feelings of stress are two-fold. First, emotional 'comfort feeding' when used repeatedly results in primarily abdominal obesity because of the greater sensitivity of abdominal adipose tissue to the combined signals of insulin and GC [95]. Second, and perhaps more importantly, it might serve in some individuals to relieve the stress-induced mental discomfort to the extent that conscious thought about how to cope with the stressor does not occur. Once stress-induced feeding becomes habitual, the problem-solver, executive part of the prefrontal cortex might no longer be actively engaged in the outcome; 'comfort food' intake can become a reflex. However, it is clear that conscious use of the prefrontal cortices can, with work, abrogate bad habits. This fact forms the basis for meditational and mindfulness exercises used by many [96,97].

Stress-induced obesity: a cultural paradox

Given that feeding is essential for life, and that energy stores are required for both finding food and for cognition and planning to allow escape or travel to sites with more food (flight) or warring with neighbors for food (fight), it is not surprising that neural networks that subserve feeding and stress responses appeared in early life forms [98]. The impetus provided by GCs, and the bias that insulin provides to pursue more pleasurable foods that, in excess, can be stored by the same hormones, is a reasonable solution to caloric scarcity. During human evolution, food was scarce, and life-threatening stressors were frequent; GCs were probably frequently elevated and insulin was relatively low, except when feeding. It is probable that during those times there was little to no obesity.

In our current conditions of plentiful, palatable and easily accessible food, together with the proliferation of social stressors, there is increased stressor-associated non-homeostatic feeding. This causes obesity and associated hypersecretion of insulin. However, eating highly palatable foods also appears to decrease the feeling of stress and this can reinforce subsequent eating of pleasurable foods when the emotional self feels uncomfortable. It is probably not a healthy thing to do and can decrease longevity; reducing caloric intake by ~30% below normal extends the lifespan and reduces disease in monkeys and other mammals [99]. Thus, to extend our health and lifespan, it makes sense to markedly reduce our total food intake, and particularly our intake of snack and prepared foods that are high in palatable calories. With that said, however, relieving an occasional intense feeling of stress by eating something pleasurable does not cause obesity; however, habitual relief of life's discomforts using this means inevitably leads to obesity.

It seems of critical importance then, with regard to the current obesity epidemic, to deliberately increase training of our cognitive, executive prefrontal brains to overcome emotional, habitual responses, using techniques such as mindfulness and meditation, to become, be and remain aware of those habits that, although acquired easily, strongly reinforce stress-induced eating. Such individual practices, or even public health programs that are centered on focused mindfulness training might modify some of the stress-induced eating habits that contribute to the current epidemic of obesity.

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