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Excessive Consumption of Sugar: an Insatiable Drive for Reward

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Abstract

Purpose of Review Eating behavior provides energy to ensure proper functioning of the organism. Reward aids in seeking foods that bring energy and pleasant taste, whose consumption is safe. As evidenced by the obesity "epidemic" which largely stems from overeating, reward becomes a detriment when palatable tastants are available in unlimited quantities. This review presents recent evidence on mechanisms underlying palatability-driven excessive consumption of sugar.

Recent Findings Appetite for sugar is propelled by changes in the morphology and activity of the reward system reminiscent of addiction. Sugar intake also shifts the hunger-satiety continuum, facilitating initiation of consumption in the absence of energy needs and maintenance of feeding despite ingestion of large food loads that endanger homeostasis.

Summary Ingestion of excessive amounts of sugar relies on triggering mechanisms that promote addictive-like behaviors, and on overriding neuroendocrine signals that protect internal milieu.

Keywords Reward · Sugar · Sweet · Addiction · Withdrawal · Adolescent

Introduction

At the end of a feast, one does not eat chocolate cake due to energy needs. But, one may be "hungry" for dessert. Our laboratory has argued that hedonic deprivation, that is hunger for palatable foods, can lead to similar changes in opioid gene expression observed with energy deprivation [1]. But, it should be noted that palatability is plastic. A bowl of oatmeal would not be attractive to most individuals following a feast, but if an individual is energy-deprived, serving of oatmeal would be very palatable/desirable.

A host of studies have evaluated the neural circuits involved in sweet taste preference [2]. Sugar intake can alter the activity of neuroregulators, and likewise, neuroregulators can affect sugar intake. For example, chronic consumption of sugar can make rats more sensitive to the discrimination of a mu opioid ligand [3]. Another example is that sugar consumption can decrease pain perception in human infants [4]. On the other hand, administration of a variety of neuroregulators can affect both motivation to eat sweet tastants and absolute intake of such foods [2]. The intimate involvement of sweet tastants in neural circuits associated with reward has led to the idea that sugars might be addictive. In fact, the circuits that respond to sweet taste overlap with those involved in drug abuse and other addictive behaviors [5]. During the past decade, a variety of reviews have either supported or dismissed the notion of "sugar addiction" [5–7].

Prior to delving into processing that occurs at the level of reward circuitry, we begin this review by focusing on the functional relationship between the "homeostatic" system, classically viewed as regulating mainly eating for energy, and sugar consumption. This relationship is particularly crucial as overconsumption of calories from sugar might pose a danger to the internal milieu resulting in a range of consequences, from short-term physicochemical changes to long-term threats on health.

Functional Relationship Between Energy Balance Neuroregulators and Sugar Intake

Data suggest that excessive sugar intake is facilitated by two key factors. On the one hand, it is possible thanks to adaptive

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neuroendocrine changes within the hunger-satiety continuum to motivate an organism to consume sugar even in the absence of energy deprivation. On the other hand, while seemingly unlikely, orexigens typically involved in eating for energy tend to promote intake of palatable foods independent of these tastants' caloric density and also independent of the energy status of the organism.

Ghrelin, an orexigenic peptide synthesized mainly in the stomach and also in select CNS neuronal populations, is often associated with eating due to energy needs and energy homeostasis in general. However, there is a large literature indicating that ghrelin also is involved in reward-induced feeding [8]. Aside from targeting hypothalamic and brainstem areas involved in feeding, it binds to the growth hormone secretagogue receptor (GHSR) in the ventral tegmental area (VTA), nucleus accumbens (NAcc), and septum, amongst others [9]. When ghrelin O-acyltransferase (GOAT), the enzyme which results in biologically active ghrelin, is knocked out (KO) in mice, the KO animals show reduced food intake and resistance to obesity when fed a high-fat/high-sugar or medium-chain triglyceride/high-sugar diet [10]. Ghrelin induces food-reinforced behavior in the mesotelencephalic reward pathway, and this effect is mediated by dopamine [11]. VTA and dorsal lateral septum administration of ghrelin increases motivated behavior for sugar reward, as assessed in an operant conditioning paradigm in rats [12, 13]. Skibicka et al. proposed that aside from relying on the opioid circuit to increase food reward, ghrelin stimulates palatability-driven consumption by engaging neurons synthesizing one of the most potent promoters of eating for energy, neuropeptide Y (NPY) [14]. In a state of overnight food restriction, associated with higher levels of endogenous ghrelin, VTA ghrelin receptor blockade was sufficient to decrease motivation to work for reward [12].

Studies on the aforementioned hypothalamic peptide, NPY, indicate that its role in feeding regulation is more complex in the context of sweet reward than merely driving search for calories. Intracerebroventricular (ICV) NPY is well-known to increase animals' preference for carbohydrates over a high-fat or high-protein diet [15]. ICV NPY in nondeprived rats stimulates consumption of sucrose and saccharin solutions in single-bottle tests. When sucrose solutions flavored with Kool-Aid were selectively associated with NPY injection during single-bottle training sessions, subsequent two-bottle preference tests showed a significant shift in preference toward the flavor of sweetened water paired with NPY during training [16]. Thus, NPY enhances ingestion of sweet solutions regardless of caloric density and to potentiate sweet taste preference via an associative mechanism. In line with those findings, Pandit et al. infused NPY into the lateral hypothalamus (LH), NAcc shell, and VTA, and reported that motivation for sucrose (assessed using a progressive-ratio schedule of reinforcement) increased after VTA and NAcc administration, whereas NAcc shell or LH infusions of the peptide also increased sucrose consumption. Interestingly, the effect of VTA NPY on motivation for sugar was attenuated by dopamine receptor blockade, which indicates NPY's ability to act as a trigger for reward [17]. Furthermore, rats given access to a free-choice high-fat high sucrose (HFHS) diet for 1 week, hypothalamic NPY mRNA levels were upregulated [18]. Finally, NPY gene expression was also increased in the brain stem of rats after 2 weeks of scheduled access to a high-sugar meal, which underscores the involvement of NPY in propelling consumption of sucrose [19].

A similar relationship between sugar intake and a "classical" orexigen has been found in the context of Agouti-related protein (AgRP), an endogenous antagonist of melanocortin (MC) receptors. Gaysinskaya and colleagues found that a sucrose compared to starch preload in rats produced AGRP and NPY mRNA changes that parallel those observed just before a meal after longer food deprivation [20]. ICV AGRP was determined to increase operant responding for sugar, and this effect was blocked by pretreatment with the dopamine receptor antagonist, α-flupenthixol [21]. A synthetic MC-4 receptor antagonist, SHU9119, injected directly in the VTA increased operant responding for sucrose pellets under fixed ratio, but not in progressive ratio schedules [22•]. Davis et al. reported that ICV AGRP enhanced neuronal activation in midbrain dopamine neurons and dopamine turnover in the medial prefrontal cortex. It also attenuated acquisition of a conditioned place preference for sugar [23].

One should note that short-term access to palatable diets inhibits electrical activity of hypothalamic NPY and AgRP neurons, and enhances activity of neurons synthesizing anorexigens, such as POMC and CART [24]. NPY and AgRP levels return to baseline after a 7-day continuous exposure to rewarding food [25]. It seems therefore that very short-term, episodic access to sugar (and to other palatable ingestants, including fat) does not cause dysregulation of the homeostatic system or the functional "reassignment" of systems that control eating for hunger to stimulating eating for pleasure. Instead, chronic intake of rewarding foods leads to changes in those orexigenic mechanisms that typically facilitate hunger responses. In line with that, NPY mRNA was overexpressed in the hypothalami of rats even after transfer from long-term consumption of palatable diets to regular chow, and animals switched from HFHS diets to standard food and then back to palatable food were found to overeat immediately upon reintroduction of tasty ingestants [26].

While enhanced activation of orexigenic mechanisms promotes overconsumption driven by palatability, it is interesting that potent anorexigenic systems seem incapable of preventing excessive sugar intake which is at times so high, due to, e.g., extreme stomach distension or elevated osmolality that it endangers internal milieu. It is also striking that dessert presentation counteracts satiety seemingly reached after a meal and that suddenly discontinued presentation of

habitual dessert (resulting in hedonic deprivation) lowers subjective post-meal fullness. In line with these observations, forced abstinence from palatable food leads to lower expression of anorexigenic CART and brain-derived neurotrophic factor (BDNF), possibly impairing satiety and making it more likely that an individual will continue searching for food [26]. CRH mRNA levels in the amygdala and paraventricular hypothalamic nucleus (PVN) are reduced by extended exposure to a palatable diet, consistent with decreased satiety, and elevated in the amygdala during withdrawal from this diet, which might contribute to heightened motivation to search for sugar [27, 28].

One of the most compelling sets of results shedding light on the complexity of reciprocal functional relationship between a CNS anorexigen and appetite for sugar comes from research on oxytocin (OT). This nonapeptide, synthesized primarily in the PVN and supraoptic (SON) nuclei and released throughout the CNS as well as—via the neurohypophysis—into the general circulation, promotes termination of consumption [29]. OT release has been associated with elevated osmolality, with increase in select nutrient levels, and upon ingestion of large food loads (as well as excessive stomach distension in general) [30–34]. Increased c-Fos immunoreactivity in OT neurons and high OT plasma levels coincide with meal termination. Injections of OT in the cerebral ventricles as well as in numerous brain sites, including the hypothalamus and the limbic system, produce cessation of feeding [35–40]. Importantly, OT administration in the reward system potently decreases consumption of sweet carbohydrates and saccharin, whereas antagonism of the OT receptor increases intake of sugar [36, 38, 39]. Accordingly, genetic deletion of OT in mice leads to excessive consumption of sucrose and other sweet ingestants, and this effect persists regardless of short- or long-term access to sweet diets [41]. Yet, despite this profound involvement of OT in the regulation of sugar (and food) consumption, habitual overconsumption of sweet foods occurs commonly. One of the processes that facilitates this overconsumption might rely on OT system's activity being down-regulated upon long-term intermittent sugar exposure. Mitra et al. gave male rats 20 days of scheduled access to a sucrose vs cornstarch. On the final day, activity of OT neurons (defined through colocalization with c-Fos) at the end of a meal was blunted in animals that had extended access to sucrose compared to cornstarch [42]. Interestingly, low OT neuronal activation was also seen in animals chronically exposed to sucrose than on the experimental day received a cornstarch meal. It has been proposed that elevated opioid tone driven by sugar intake might be responsible for suppressing activation of OT cells. Indeed, pre-treatment with an opioid receptor ligand, butorphanol tartrate, blunts meal-end activation of PVN OT neurons in animals given short-term, episodic (rather than chronic) access to sucrose [43]. Conversely, OT even at subthreshold doses is particularly effective at suppressing butorphanol-induced hyperphagia [44]. Interestingly, opioid receptor activation (including with butorphanol) significantly decreases responsiveness of PVN and SON OT cells to administration of a nausea and gastrointestinal discomfort inducing anorexigenic agent, LiCl, and prevents acquisition of conditioned taste aversions to sweetened solutions [45]. It can be proposed that one consequence of action of opioids in the context of delaying termination of eating for palatability is that they prevent avoidance of foods that taste good, but whose intake in larger quantities leads to emesis, malaise, and threats to internal milieu.

Overall, it appears that excessive consumption of sugar is facilitated by a shift in a hunger-satiety continuum that propels an individual to feel hungry for sugar despite a lack of an actual energy deficit, and reaches satiety later, thereby promoting maintenance of consumption even in the face of negative consequences.

Reward Processing of Sugar Consumption

The aforementioned adaptations in hunger and satiety mechanisms enhance the capacity to ingest large amounts of sugary foods by overriding homeostatic signals. On the other hand, the reward system shapes feeding behavior to promote the repeated intake and seeking of high-sucrose foods. Reflecting this notion, both short- and long-term sucrose intake affects gene expression and neuroplasticity in the brain, and binge-like consumption of sugar facilitates dopamine release in the NAcc similar to that of drugs of abuse [46, 47]. Specifically, palatable foods, including high-sugar ingestants, result in dopamine release in the NAcc in laboratory animals [48] and the dorsal striatum in humans [49]. Release of dopamine in the dorsal striatum also occurs in rats seeking drugs [50].

It is well documented that opioid agonists increase feeding and antagonists decrease feeding. Some studies suggested that opioids might control intake of specific macronutrients, namely fat; however, Gosnell et al. demonstrated that opioids increased intake of preferred macronutrients by an individual, and those include sugar [2, 51]. Many studies by Levine and colleagues showed that the opioid antagonists naloxone or naltrexone preferentially decreased intake of highly palatable foods, at doses much lower than observed with bland laboratory chow [51]. Caref et al. [52] have recently reported that endogenous opioids in the NAcc promoted approach to palatable food even in rats that were not in need of calories. While opioids affect intake for palatability, ingestion of preferred tastants affects opioid-related circuits and behaviors. Intake of highly palatable food results in increased mu receptor gene expression in a variety of brain sites, perhaps reflecting reduced peptide release and/or compensatory down-regulation [2]. Chang et al. [53] measured fat intake over a 5-day period

and selected those animals that had preference for a high-fat diet. They found increased proenkephalin expression in the PVN, NAcc, and central nucleus of the amygdala in the fat preferring rats maintained on chow for 14 days. Also, Osborne-Mendel rats which demonstrate diet-induced obesity have increased levels of mu opioid receptor mRNA in the hypothalamus compared to rats which are resistant to diet-induced obesity [54]. It should be noted, therefore, that molecular and behavioral consequences of palatable (including, sugary or fat) food consumption appear to be greatly affected by inherent or acquired preference, and this aspect of the regulation of feeding reward has been oftentimes overlooked.

Activation of the dopamine and opioid systems upon sucrose ingestion produces addictive-like behaviors and binge eating. Since sugar intake is mediated by brain sites and molecular systems also involved in drug abuse, the question arose as to whether discontinuation of habitual sugar consumption produces some of the withdrawal effects observed post-drug taking. It has been found that withdrawal symptoms after cessation of prolonged sucrose consumption in rats include depression- and anxiety-like behaviors. Interestingly, animals exposed to a high-sugar diet for an extended period of time, followed by exposure to only standard chow, consume very few calories and lose weight. Upon regaining access to a high-sugar diet after weeks of forced abstinence, animals demonstrate increased lever pressing for the palatable tastants [46]. One mechanism that promotes food reward and mediates withdrawal symptoms such as anxiety and depression is facilitated by D1 receptor-expressing medium spiny neurons (MSN) in the NAcc. Activation of these neurons increases food intake, while inhibition decreases consumption. Studies on other drugs of abuse, such as cocaine, nicotine, and amphetamines, have revealed that long-term exposure causes changes in MSN morphology, specifically increased dendritic density and complexity in the NAcc, which have been well-characterized [55–59]. Similarly, long-term sucrose exposure changes MSN morphology by reducing dendritic length but increasing dendritic density at distal branches. Notably, this only occurs in the NAcc shell but not the core, which is consistent with numerous injection studies, in which exogenously administered mediators of reward have been found to produce increases in consumption of palatable diets [21, 60–62] only after injection into the NAcc shell. Furthermore, dopamine release is prolonged and reuptake delayed in animals exposed to sucrose long-term, promoting overconsumption. Upon fasting after long-term sucrose exposure, anxiety and altered dopamine and acetylcholine levels were observed in rats, thereby paralleling the effects of opiate withdrawal [46]. It should be emphasized that dopamine increases cytosolic cAMP levels, leading to the activation of protein kinase A (PKA) and phosphorylation of various intracellular targets, such as dopamine-and cAMP-regulated phosphoprotein-32 (DARP-32) and cAMP response element binding (CREB) protein, altering cellular function [63]. Inactivation of CREB during sucrose deprivation correlates with increased expression of a specific K+ channel, Kir2.1, which induces hyperpolarization of membrane potentials and reduced firing of action potentials. This decrease in membrane excitability leads to anxiety-like behaviors in rats [64••, 65, 66]. Furthermore, overexpression of Kir2.1 in D1r MSNs alone is sufficient to induce the same behavioral effects in animals [64••].

The changes in the reward system described above occur regardless of the developmental stage of the organism. From addiction-related studies, it is well-known that exposure to alcohol [67, 68] and drugs of abuse [69, 70] during adolescence, a time of extensive neural development with heightened plasticity sensitive to neural insults [71•], profoundly impacts adult reward-related behaviors and neural responses [72]. Considering that sugar consumption and drug taking produce some degree of overlap in neural responses, one pressing question is whether there are any similarities in untoward long-term effects of sugar consumption early in life. Particularly, it has been proposed that a possible consequence of early habitual and excessive consumption of palatable sugars with the resulting adaption in reward circuits (e.g., dopamine) might be altered hedonic processing (arguably somewhat resembling "tolerance" to the effects of sugar) during later stages of life [73, 74].

For example, Naneix and colleagues [75••] found that continuous access to a 5% sucrose solution for 16 days in adolescent rats (postnatal 30 days [P30] onwards) induces behavioral changes characteristic of anhedonia in adulthood. Oral delivery of palatable sucrose or saccharin to adult controls without prior extended exposure to those tastants in adolescence generates a higher rate of positive orofacial responses. Importantly, fewer positive and more neutral or negative responses are displayed by the sucrose-exposed animals. This was paralleled by significantly lower c-Fos immunoreactivity in the NAcc in the sucrose non-naïve rats. Building on these findings, Gueye et al. and Vendruscolo et al. [76, 77] showed reduced preference for palatable solutions and altered motivation parameters in animals subjected to the same sugar exposure paradigm. In instrumental conditioning, adults previously exposed to sucrose showed reduced adaptability in switching from a fixed ratio (FR) of one to five for saccharin reward as well as lowered break point in a progressive ratio (PR) schedule, the results being consistent with previous studies (e.g., [77]). Interestingly, both research groups [76, 77] examined performance of these rats in the forced swim tests and found increased immobility in the animals with adolescent sucrose consumption compared to the sucrose-naïve group. Antidepressant treatment successfully reversed the outcome. Adolescent chronic sugar exposure therefore appeared to produce an adult depressive phenotype of anhedonia, reduced motivation, and an increased passive coping strategy. The underlying molecular mechanism for this phenomenon was

found to be mediated through the aforementioned MSNs expressing the D1 receptor. Exposure to sucrose increases dopamine signaling in neurons targeting the NAcc shell, and prolonged binge-like sucrose consumption causes a change in morphology in these neurons. These changes include a decrease in total dendritic length of NAcc shell MSNs through reduced distal dendritic complexity [78••].

Anhedonic and depression-like phenotypic features, including motivational deficits, in adult animals that had been chronically exposed sugar in adolescence, have been associated with maladaptations in the reward circuit [79•]. Function and maturation of the DA system during adolescence appear to be especially vulnerable in the face of chronic consumption of palatable foods [80–83]. Dopamine receptor 1 (D1) agonism increases, whereas antagonism decreases, breakpoints in control rats in the PR task. Sucrose-exposed animals remain mostly unaffected by both treatments, with only the highest dose of the antagonist decreasing the breakpoint. Lowered sensitivity to both the dopamine receptor 2 (D2) agonist and antagonist was also noted amongst the sucrose group. Naneix et al. [79•] also found reduced D1 and D2 mRNA and protein content in the NAcc. Reduced behavioral sensitivity to dopaminergic drugs and lowered expression of dopamine receptors brought on by extended adolescent sugar diet suggests that modifications to the dopamine system could underlie anhedonia and depressive phenotype in adulthood. As the dopamine system does not work in isolation during sugar-induced reward, but rather in concert with opioid and endogenous cannabinoid systems [84, 85], a possible link between the adolescent dietary history and other molecular components of the reward system requires further study.

One poorly understood yet crucial aspect of the current state of knowledge is that the impact of chronic exposure to sugar on motivation appears to be sex-specific. Reichelt et al. [86•] observed that daily 2-h access to 10% sucrose for 28 days (starting on P27), a paradigm promoting binging and habitual consumption [87, 88], reduced PR breakpoint amongst sucrose-receiving males compared to controls, whereas breakpoints were higher in females with adolescent sucrose exposure. One possible explanation is that those higher breakpoints result from enhanced cravings [89, 90], which typically accompany negative mood and depression in females [91].

Data from human studies suggest that habituation to sugar influences reward signaling in adolescents. In the fMRI studies, Burger and Stice [92] observed that, compared to non-habitual drinkers, adolescents consuming high levels of Coke who were shown the Coke logo as a cue had increased activity in the posterior cingulate cortex and decreased activity in the ventromedial prefrontal cortex. This outcome parallels the results obtained in earlier studies on overweight youths' responsivity to food product logos [93]. The change in the posterior cingulate cortex likely promotes enhanced salience [94, 95] to the logo as a conditioned cue amongst drinkers, whereas the decrease in the ventromedial prefrontal cortex is speculated to increase the likelihood of excessive consumption due to this site's role in inhibition in decision making and self-control [96, 97]. A subsequent study by Burger [98•] established that young adults (mean age 23 years) exhibit reduced dorsal striatal response during consumption of a high-sugar drink for as many as 21 days. Reduced activity of the ventromedial prefrontal cortex, a region associated with habitual-based decision-making, is seen during anticipation of consumption [99, 100]. Shearrer et al. ([101••]) examined BOLD patterns amongst at-risk adolescents during palatable milkshake consumption vs noncaloric, tasteless solution. They found that higher sugar content of the milkshakes produced the higher response of gustatory and hedonic regions (the caudate, central operculum, superior temporal gyrus, juxtapositional lobule, and thalamus). Overall, habitual consumption of sugary tastants during adolescence appears to influence both rewarding properties of sugar and reward-related salience and decision-making parameters. Though a possible effect of adolescent consumption of sugar on behavioral and neural responsivity to palatable ingestants later in adulthood remains elusive, longitudinal studies on excessive appetite and overweight provide indirect support to the hypothesis that early exposure to chronic food reward through poor diet, coupled with genetic predisposition, greatly increases the risk of developing obesity later in life [102–105].

Conclusion: Sugar Consumption as an Insatiable Drive for Reward

Having evolved in an environment where resources are scarce, we rely on evolutionarily conserved feeding regulatory mechanisms that propel us to obtain high-energy foods that can be safely consumed even in large quantities. High-sugar ingestants are highly preferred. In the current obesogenic environment in which readily available sugars are overconsumed to the point that endangers our health, these mechanisms are not an asset, but rather a basis of aberrant appetite and metabolic processing. Consequently, not only does the intake of sweet (and palatable, in general) diets lead to addiction-like molecular and cellular changes in the reward system that propel habitual consumption, but it also hijacks the hunger-satiety continuum by shifting it toward perpetual hunger and weakened satiety. One can argue, therefore, that the current obesity "epidemic" which stems to a large extent from excessive consumption of highly palatable and caloric sugary foods, pharmacological strategies to curb overeating should be combinatorial and rely on simultaneous targeting of the complex mechanisms triggered by sugar, including reward, satiety, and hunger.

Compliance with Ethical Standards

Conflict of Interest Pawel K. Olszewski, Erin L. Wood, Anica Klockars, and Allen S. Levine declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- •• Of major importance

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