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Review

Recent studies of the effects of sugars on brain systems involved in energy balance and reward: Relevance to low calorie sweeteners

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HIGHLIGHTS

- Sugar intake differentially affects the homeostatic and hedonic pathways.
- Homeostatic and hedonic neural systems interact in response to sweetener intake.
- Low calorie sweetener use has become increasingly popular.
- Low calorie sweeteners have also been shown to affect both the homeostatic and hedonic neural systems.

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ABSTRACT

The alarmingly high rates of overweight and obesity pose a serious global health threat. Numerous factors can result in weight gain, one of which is excess consumption of caloric sweeteners. In an effort to aid weight loss efforts, many people have switched from caloric sweeteners to low calorie sweeteners, which provide sweet taste without the accompanying calories. In this review, we present an overview of the animal literature produced in the last 5 years highlighting the effects of sugar consumption on neural pathways involved in energy balance regulation and reward processing. We also examine the latest evidence that is beginning to elucidate the effects of low calorie sweeteners on these neural pathways, as well as how homeostatic and hedonic systems interact in response to, or to influence, sugar consumption.

Contents

Despite numerous adverse health consequences associated with excess body weight, including increased risk of type 2 diabetes, hypertension, and heart disease [1,2], rates of obesity and overweight continue to rise on both the national and global level [3]. Today, approximately 70% of American adults are classified as overweight or obese [4]. Excess weight gain is multi-determined and has been attributed to such factors as genetic susceptibility and sedentary lifestyle [5–9]. In addition, over the past several decades, the food landscape has shifted dramatically, and highly palatable, highly processed foods are now ubiquitous for most individuals [10]. Many such food options, including breakfast cereals, "nutrition" bars, cakes, condiments, flavored yogurts, and beverages like soda and sports drinks, contain high amounts of added sugars. Increasing evidence suggests that sugar consumption contributes to the current obesity epidemic [11–16], prompting the World Health Organization to create guidelines recommending children and adults reduce their intake of added sugars [17].

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Given associations between excess sugar intake and the current crisis of obesity, several lines of research have been devoted to examining how sugars affect neural pathways implicated in energy intake and reward. A network of complex signals within the brain serve to regulate energy intake; the homeostatic system regulates feeding based on energy need, while hedonic eating behavior is primarily thought to be driven by neural systems associated with pleasure and reward [18]. In laboratory animals, self-administration of sugar has been shown to activate both the homeostatic and hedonic pathways [19].

Not surprisingly, low calorie sweeteners have become increasingly popular over the years as a means to facilitate weight loss efforts as well as to aid individuals with diabetes to obtain euglycemia [20]. Unlike sugars, such as sucrose, high-fructose corn syrup, and glucose, which contain calories, low calorie sweeteners provide sweet taste with little to no calories. Low calorie sweeteners are often used in "diet" food items to maintain taste while decreasing a food or beverage's caloric value. Examples of low calorie sweeteners include saccharine, aspartame, neotame, acesulfame potassium (Ace-K), sucralose, and advantame. Low calorie sweeteners are also sometimes used in combination with sugars.

Although the literature is replete with information regarding how low calorie sweeteners affect the taste signaling pathway [21–24] and gut microbiota [25–27], less is known about the effects on brain reward systems. However, in order to understand the effects of low calorie sweeteners on reward pathways, it is important to understand the ways in which natural forms of sugar act on these neural circuits as a point of comparison. Therefore, the purpose of this review is to present recent data published over the last 5 years from the laboratory animal literature illustrating the effects of sugar intake on both select homeostatic and hedonic neural systems, as well as evidence demonstrating how these two separate systems interact. Finally, we review recent findings from the preclinical and human literature demonstrating the effects of low calorie sweeteners on these same pathways.

1. Effects of sugars on "homeostatic" neural systems

The homeostasic system, which regulates feeding patterns based on energy need, is composed of two antagonistic pathways. The orexigenic pathway includes neuropeptide Y (NPY) and agouti-related protein (AgRP), which are known to stimulate food intake [28] and are produced in the arcuate nucleus (ARC) of the hypothalamus, a critical region involved in homeostatic energy balance [29]. In contrast, the anorexigenic pathway, including proopiomelanocortin (POMC) neurons produced in the ARC, has the opposite effect by inhibiting food intake [28].

Recent evidence suggests that sugar intake differentially affects these two opposing pathways. After a sucrose preload, mice consumed more chow and this behavioral change was accompanied by variations in NPY and AgRP. Immediately following the preload, mice showed reduced expression of NPY and AgRP in the ARC. However, 30–60 min after the sucrose preload and right before the chow meal, mice showed a marked increase in both [30]. This suggests that sucrose consumption led to a temporary decrease in orexigenic peptides followed by activation of the orexigenic pathway, potentiating caloric consumption. In another recent study, mice maintained on a high fat diet and given limited access to sucrose-sweetened water (SSW) showed a down-regulation of POMC mRNA expression in the hypothalamus. In addition, these mice consumed greater amounts of the high fat diet on days that the SSW was available, suggesting that this reduction in satiety signaling may have facilitated hyperphagia in this group [31]. Chronic limited consumption of a high sucrose diet has also been shown to lead to decreased activity of the anorexigenic oxytocin system in the hypothalamus, which has been associated with satiety and meal termination [32].

Recent data indicate that the type of sugar ingested plays an important role in satiety. One animal study comparing the effects of 24 h access to sucrose, glucose, fructose, or high-fructose corn syrup found that glucose led to a marked upregulation of the satiety-inducing hormone, cholecystokinin (CCK), within the hypothalamus, while fructose resulted in a downregulation of this peptide [33]. This suggests that, relative to fructose, glucose may be more effective in eliciting satiety. This is in line with animal research showing central administration of glucose to inhibit food intake and fructose to stimulate feeding [34]. Further, in humans, fructose ingestion to lead to lower levels of serum glucose, insulin, and glucagon-like polypeptide 1 (GLP-1), a hormone associated with increased satiety relative to glucose ingestion [35].

2. Effects of sugar on "hedonic" neural systems

Given that sweet foods and beverages are generally considered pleasurable, the effects of caloric sweeteners on brain mechanisms associated with processing reward, such as the mesolimbic dopamine (DA) system and opioid systems, have been an area of intense research in recent years. One such study observed decreased striatal DA concentrations following prolonged access to a sucrose solution in high-sucrose drinking rats [36], a finding also reported by this group in response to chronic exposure to ethanol [37]. Expression of tyrosine hydroxylase (TH), an enzyme involved in DA synthesis, was also decreased in the striatum of high sucrose-drinking rats. Acute increases in DA release upon consumption of palatable food may, as the authors posit, initiate a negative feedback cycle, inhibiting DA synthesis, ultimately leading to both reduced TH expression and striatal DA concentrations. It is important to note that while reduced DA content may reflect neuroadaptations due to prolonged sucrose consumption, reduced DA has been observed in the nucleus accumbens (NAc), a brain region associated with reward, of rats prone to obesity even prior to excessive weight gain [38]. Thus, it is also possible that reduced striatal DA concentrations may have predisposed the animals to excessive sucrose consumption, especially as only high-drinking rats were studied. Finally, in this study, high sucrose-drinking rats showed increased prolactin expression. Given the role of DA in inhibiting prolactin, reduced DA concentrations may have led to elevated prolactin.

Two recent studies have also explored the acute effects of sugar consumption on DA levels within the two subregions of the NAc, the shell and the core, given differential efferent projections from these regions. Rewarding substances such as drugs of abuse are known to elevate DA within the NAc shell and this response is thought to facilitate strong associations between the reward and related cues [39]. Using fast-scan cyclic voltammetry in food restricted rats, Cacciapaglia, Saddoris [40] found that sucrose-related cues lead to increased DA levels in both subregions of the NAc, however, DA levels were greater and sustained for longer in the shell. Increased DA levels were also observed in the NAc shell, but not the core, after lever pressing for sucrose. Together, these experiments implicate DA within the NAc shell, versus the core, in sucrose reward. Using microdialysis techniques in food-restricted animals, it has also been shown that while novel exposure to sucrose increases DA levels in the NAc shell, this effect wanes with repeated exposure, in contrast to what is seen with drugs of abuse [41]. Notably, rats trained to respond for sucrose did not show habituation of increased DA levels in the shell. This group also noted elevated DA levels in the shell, but not core, when animals responded for sucrose as well as in response sucrose-related cues during extinction. Interestingly, however, elevated DA levels were observed in both the shell and core regions when sucrose was delivered without the requirement of responding ("response non-contingent" sucrose feeding).

Given the established role of opioid signaling in hedonic processes [42], recent studies have also explored opioid involvement in the rewarding aspects of sugar consumption. Interestingly, Ostlund, Kosheleff [43] found no differences in sucrose intake during acquisition testing between mu-opioid receptor knockout (MOR KO) and control mice. However, MOR KO mice showed fewer average bursts of sucrose licking