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Chapter 6

Artificial Sweeteners in Animal Models of Binge Eating

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i. Summary/Abstract

Rising rates of obesity in most industrialized countries are a major cause of serious medical conditions, including diabetes, heart disease, and mental health disorders. Binge eating, characterized by excessive consumption of highly palatable food within a short period of time, contributes significantly to these problems, even in individuals who are not diagnosed with binge eating disorder (BED). Over the last half century, the use of non-nutritive substitutes has been promoted as a means to reduce fat and sugar consumption, potentially minimizing obesity-related illnesses. Paradoxically, increased intake of artificial sweeteners is associated with weight gain, which may be linked to alterations in metabolic processes. Artificial sweeteners also increase food intake in both humans and rodents, raising intriguing possibilities that these substances are altering biological processes that underlie the homeostatic control of feeding. We explore this idea by summarizing the clinical and preclinical literature on behavioral and biological mechanisms of artificial sweeteners. As a starting point, we review evidence that non-nutritive sweeteners are rewarding in rodent models, then provide a comparison of neural systems mediating the rewarding properties of natural and artificial sweeteners. We then summarize data pointing to sexual dimorphism in behavioral and biological responses to sucrose, with preliminary evidence suggesting that responses to artificial sweeteners may follow a similar pattern. Finally, we provide an overview of the relationship between binge eating and substance use disorders, noting findings from animal studies that artificial sweeteners could contribute to this comorbidity.

ii. Keywords:

feeding, reward, dopamine, opioid, sucrose, saccharin

1. Introduction

Binge eating disorder (BED), the most common of all eating disorders [1], is characterized by consumption of large amounts of food within a discrete period of time in the absence of compensatory behaviors [2]. According to World Health Organization estimates, the lifetime prevalence of BED is 1.9%, with a median onset age of 20 years old [3]. Not surprisingly, BED is more common in women than men, although these ratios are distributed more evenly than in other eating disorders [3]. Binge eating is highly comorbid with a number of medical conditions, other psychiatric disorders [4], and a reduced quality of life [5]. Of the medical conditions associated with BED, obesity is one of the most prevalent, likely due to the lack of purging or exercise following binge intake [6]. Adult patients with BED have significantly higher obesity rates than individuals with no eating disorder [7], and even those who are not obese are distressed by their bingeing behavior.

Many patients with obesity and BED attempt to limit caloric intake and counter weight gain by adopting hypocaloric diets, specifically restricting highly palatable foods [8]. This is generally ineffective, as individuals who are food restricted tend to binge on foods that are high in sugar and/or fat, ingesting significantly more calories than non-restricted individuals [9]. The pattern is exacerbated in modern society with the prevalence and availability of highly palatable food. Consumption of these foods activates brain reward circuits [10], increasing the probability that behaviors leading to their intake will be repeated. These factors undoubtedly contribute to growing rates of obesity [11], which have tripled since 1975 (WHO). Obesity dramatically increases the risk of medical conditions such as type 2 diabetes, hypertension, and dyslipidaemia, although these metabolic syndrome disorders may develop in BED patients, even in the absence of obesity [12].

Artificial sweeteners are an appealing alternative to restrictive diets in that they allow individuals to consume highly palatable food with minimal calories. If bingeing in humans is

a reaction, at least in part, to restriction of forbidden ‘pleasure’ foods, consumption of these commodities should reduce binge eating. Weight gain should also be minimized when individuals opt for artificial, over natural or processed, sugars simply due to a reduction in calorie intake. It is therefore surprising, that the two have grown in parallel: higher rates of obesity and higher use of artificial sweeteners.

1.1. Animal models of binge eating

Despite the prevalence and associated problems, the etiology of BED is not clearly understood [13]. Animal models provide a means to unravel the causal mechanisms of this disorder as rodents, like humans, exhibit binge eating when they are provided with intermittent access to highly palatable food or when they undergo periods of food restriction and stress [14]. The intermittent access protocol (12 hr food deprivation followed by 12 hr access to sucrose or glucose and food) simulates behavioral aspects of BED, including escalation of intake and withdrawal-like symptoms [15, 16]. This pattern reflects eating patterns of BED as patients often display excessive food intake during the evening after self-imposed restriction during the day [17]. Importantly, the rat intermittent access model produces compulsive responding for palatable food, mimicking the loss of control over food intake that characterizes patients with BED [18]. Caloric restriction, itself, is not a necessary pre-requisite for bingeing in that fat bingeing occurs when access to this commodity is limited, but regular chow is freely available [19].

Stress is also a potent trigger of binge eating, particularly when it is combined with restriction of palatable food [20, 21]. For example, manipulations, such as tail pinch, induce hyperphagic for palatable food [22] and increased consumption of standard chow [23]. Females may be more sensitive stress-induced feeding, showing more rapid increase of

palatable food intake than males [24]. Developmental factors, including level of maternal care and exposure to stressors during adolescence, also increase vulnerability to binge intake [25].

Few studies have investigated the impact of artificial sweeteners on binge eating: in most animal studies access to these substances is a control condition, used to separate intake that is driven by caloric versus hedonic properties of food [26-29]. Nonetheless, inspection of data from these control groups reveals unique patterns of intake associated with access to artificial sweeteners. For example, intermittent access to saccharin produces binge-like intake in mice [26, 29], an effect that appears to be absent in rats [18, 28]. In addition to species differences, the concentration of saccharin may be a critical factor in the elicitation of bingeing behaviour, as this was much higher in the rat experiments. Moreover, a 0.4% saccharin solution induced bingeing in rats that matched the intake of rats given access to an isohedonic sucrose solution (4%) [30]. Both groups exhibited more rapid escalation of intake than control groups given unlimited access to either solution. Importantly, either intermittent or unlimited access to an isocaloric solution, maltodextrin, that provides calories with no sweet taste did not induce binge intake. Below, we describe the rodent model of intermittent access (14) that produces binge-like eating in both rats and mice.

2. Materials and Methods

2.1 Equipment and setup

All laboratory work with animals requires an existing animal-use protocol that is issued and approved through the relevant institutional animal care committee, and is in accordance with guidelines established by the NIH Guide for Care and Use of Laboratory Animals. In the limited access protocol of binge eating, animals (mice or rats) are acclimated to the room 1 week prior to the experiment. They are maintained on a 12:12h light dark cycle under standard temperature and humidity conditions ($22 \pm 2^\circ\text{C}$, $55 \pm 1\%$ humidity). They are then habituated to single housing and to the two-bottle choice set up for a minimum of 1 week.

During habituation, weight is monitored and all animals have access to *ad libitum* water and standard laboratory chow. Animals are then weight matched into the different groups. Weight and food intake are monitored using a balance with 0.1g minimal sensitivity and solution intake is reported at 0.1mL precision.

2.2 Behavioral Procedure

Limited access protocol

Limited access to sucrose induces bingeing behavior in rodents, defined as excessive consumption within a discrete period of time (usually 1 hour). A minimum of three groups should be included to verify the experimental design. The experimental (or binge) group is provided with limited access to sucrose **and food** (10% in rats [15] and 17.1% in mice [29]). Three control groups are run in parallel: limited access to saccharin (0.1% in rats and 0.09% in mice [18, 29] to control for the sweet taste of sucrose; unlimited access to sucrose to control for sucrose exposure; and a food only group to control for limited access to a food source. An additional restricted food access group can be included in which animals have unlimited access to sucrose [26].

Mice in the limited-access group receive 4 h access to sucrose or saccharin, 2 h following onset of the light cycle every day. At the end of the 4 h, the sweet solution is removed and replaced by water. This procedure lasts a minimum of 10 days [29]. In rats, the limited-access group has intermittent access (12 h) to sucrose or saccharin, beginning 4 h after the dark cycle across a 4-week period [15]. Solution and food intake are monitored in mice at 1 h, 4 h and 24 h after the beginning of the access period; in rats, measures are recorded at 1 h, 12 h and 24 h following access. The **positions** of drinking tubes (water versus sweet solution) are changed daily to avoid any side preference bias. Weights are monitored daily, prior to the sucrose or saccharin access.

2.3 Data Analysis

Consumption of food, water, and sweetened solutions should be presented as a percentage of body weight, particularly as baseline differences in this measure be related to sex, genotype, strain, or other variables of interest. Consumptions are either analyzed by 2-way repeated measures analysis of variance (ANOVA) with time as the repeated measure and group as between subjects' measure [15] or by using a Linear Mixed Model (LMM) in which consumption is assessed as a function of group, day and weight [26]. This is followed up by a post hoc analysis to assess significant differences among the groups

3. Artificial sweeteners

3.1 History of artificial sweeteners

Figure 1 provides a brief overview of the history of natural and artificial sweetener use in Western countries. Artificial sweeteners were introduced to the public on a large scale to deal with sugar rationing during WWII. The use of these compounds expanded in the latter part of the 20th century to address growing rates of obesity, which are often attributed to the overconsumption of added sugars. Health directives generally recommend a maximum sugar consumption of 10% of total calorie intake per day [31, 32], whereas most adults in industrialized countries consume between 15% and 21% of their daily calories in sugar. The proportion of sugar intake in children is even higher (16%-26%) [33]. Fructose may be a primary culprit in sugar overconsumption, particularly with the increased use of high fructose corn syrup as a sweetener beginning in the 1970s [34]. Fructose is particularly detrimental to secondary medical conditions, such as diabetes, because it increases insulin resistance, oxidative stress, and inflammatory responses [35].

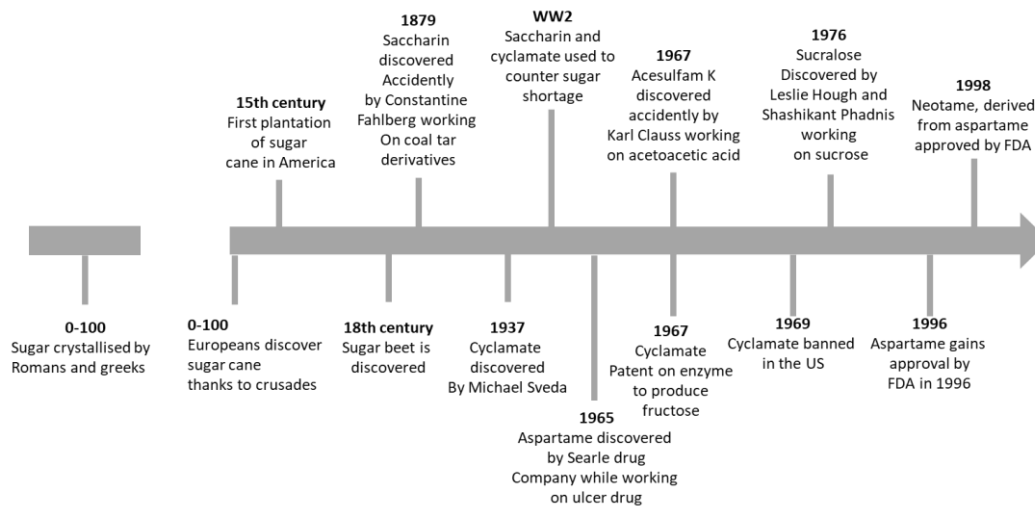


Figure 1. Historical timeline of natural and artificial sweetener availability

Non-nutritive sweetener	Sweetening strength compared to sugar
Acesulfame Potassium	200x
Aspartame	200x
Cyclamate	40x
Neotame	8000x
Saccharin	300x
Sucralose	600x

Table 1 Relative sweetening strength of non-nutritive sweeteners

Note: In animal studies, the concentration of a sugar solution is usually 4% - 20%.

3.2 Paradoxical effects of artificial sweeteners

3.2.1 Artificial sweeteners and weight gain

Despite the apparent appeal, widespread use of artificial sweeteners has not been associated with reduced obesity. Indeed, a number of studies indicate that these substances are linked to both weight gain and metabolic disorders [36, 37]. For example, a prospective study of male and female participants who normally consume artificially sweetened beverages revealed a positive correlation between the quantity of beverages consumed and weight gain over time, although the effects were not sweetener specific [38]. The findings were confirmed in a separate study, which also showed that weight gain was independent of the macronutrient content of meals. More specifically, both male and female participants using artificial sweeteners consumed the same amount and type of food as a control group (not consuming artificial sweeteners), but still gained weight [39]. Although intriguing, these findings require further investigation, particularly as serving sizes in each study were not reported.

More in line with conventional thinking, other studies report stable or decreased weight in individuals who consume artificial sweeteners [40]. This could reflect the fact that people who use artificial sweeteners are often on a weight loss diet, thereby attempting to reduce the number of calories they consume. Indeed, weight loss was observed in an intervention study in which male and female adults followed a 12-week diet, with half of the participants drinking beverages with non-nutritive sweeteners daily (701 mL) and the other half consuming the same amount of water. Moreover, other measures such as systolic pressure, waist circumference, and blood triglycerides improved in the group consuming artificial sweeteners compared to their water consuming counterparts [41]. At least in these conditions, non-nutritive sweeteners appear to be beneficial in reducing problems associated with overeating.

The impact of artificial sweeteners on weight gain is also controversial in children, with some studies reporting a positive correlation between diet soda consumption and body mass index [42], although the effect may be limited to males [43]. The findings should be

viewed with caution as children who drink a lot of sodas also tend to eat more junk food and be less active [44]. Indeed, a controlled randomized trial (over 600 healthy children followed for 18 months) found a significant reduction of weight gain and body fat mass in a group that was instructed to consume sugar-free beverages each day, compared to a group that consumed sugar-sweetened beverages [44]. In addition, in contrast to adults, children modify their food intake following consumption of artificially sweetened beverages [45] with the timing of the sweetener preload (lunch or snack) differentially impacting the later consumption of calories. Regardless of the mechanism, children's intake of noncaloric beverages requires further attention because consumption of these drinks often increases over time [46], and the impact of artificial sweeteners on developmental processes is unknown.

The controversy surrounding artificial sweeteners and weight gain is difficult to untangle in humans as eating is influenced by a combination of physiological, social, and subjective factors. For instance, participants consuming artificial sweeteners ingest fewer calories when they are not aware that sucrose has been replaced with a low-calorie substitute [47], but increase their calorie intake when they are informed of the substitution [48]. Of note, research studies are often funded by agencies with a potential conflict of interest (e.g., food industry) that could impact the interpretation of scientific or epidemiological studies [49]. Animal studies, which minimize extraneous factors that may impact eating in humans, can help to elucidate the relationship between artificial sweeteners and weight gain. At least some of this work supports a positive correlation between the two: rats given intermittent access to saccharin consumed more calories and gained more weight than a group given intermittent access to glucose [50]. The findings were confirmed in studies using saccharin or aspartame versus sucrose [51, 52]. Although further work needs to be done, preliminary evidence from animal studies supports the idea that consumption of artificial sweeteners is associated with weight gain.

3.2.2 Artificial sweeteners and metabolic changes

The effect of artificial sweeteners on weight gain may be related to reduced basal metabolism as post-prandial thermogenesis is lower in rats given access to a low-calorie sweetener compared to sucrose [50]. Moreover, in a mouse model of diet-induced model of obesity, animals given access to the non-nutritive sweetener, aspartame, exhibited reduced oxygen consumption during the dark phase and increased visceral fat due to hyperinsulinemia [53]. Similarly, saccharin consuming rats show a decrease in glucagon like peptide 1, an anorexogenic hormone which could explain increased food intake and increased blood glucose following a glucose tolerance test [54]. In contrast to aspartame, saccharin does not appear to affect insulin levels, although this may depend on the overall diet consumption. For example, differences in energy intake, weight gain and adiposity following saccharin versus sucrose consumption are only observed when rats have access to a high-fat diet [55].

If artificial sweeteners do impact weight gain, they may do so by altering metabolic processes in the periphery [56]. Like natural sugars, these substances activate sweet taste receptors which are located, primarily, on the tongue but are also expressed in the bladder, pancreas, and gut [57]. This provides a mechanism by which artificial sweeteners can alter metabolism. As an example, male rats provided access to saccharin exhibited reduced thermal responses compared to a sucrose group, suggesting that lower energy expenditure and storage of nutrients was responsible for the increased weight gain in these animals [50]. Interestingly, the effect of artificial sweeteners on metabolic effects may depend on the molecular structure of the substance. Both saccharin and acesulfame-k (500-fold sweeter than sucrose) stimulate glucose-induced insulin secretion and promote glucose uptake [58], as well as inducing adipogenesis and repressing adipocyte lipolysis [57]. In contrast, aspartame, which is only 200-fold sweeter than sucrose, produces the opposite effects, reducing adipogenesis by downregulating the expression of adipogenic markers. The latter effects were produced *in*

vitro, so must be replicated using *in vivo* measures [59]. These inconsistent effects of artificial sweeteners on metabolism may explain, at least in part, the contradictory findings regarding artificial sweeteners and weight gain.

3.3.3 Artificial sweeteners and eating

Any association between increased use of artificial sweeteners and weight gain is somewhat paradoxical in that individuals who substitute non- or low-nutritive sweeteners for sugary foods should be consuming fewer calories. The literature on this question in humans is controversial. Some studies show no effect of low-calorie sweeteners on appetite [60, 61], whereas others suggest that artificial sweeteners, specifically aspartame [62] and saccharin [63], reduce food intake. Again, this could be a specific effect of the sweeteners under study (aspartame and saccharin), which are less commonly used in food products today than are sucralose or acesulfame-K [40].

As with weight gain and metabolic effects, animal studies point to a positive relationship between consumption of artificial sweeteners and increased food intake. For example, rats given access to saccharin during the first 2 hours of the dark cycle exhibit a 10-15% increase in food intake, compared to rats given access to water. Sucrose produces the same effect suggesting that sweet tastes stimulate appetite, regardless of the calorie content [64]. In line with this idea, saccharin preload increases chow intake in rats [65] and even fruit flies exhibit increased food intake following access to an artificial sweetener [66].

The effect of artificial sweeteners may be exacerbated in binge eating models with food intake being higher in animals given limited access to saccharin, compared to those given limited access to sucrose [26]. This difference could not be explained, entirely, by the caloric content of sucrose (i.e., animals consuming calories in sucrose would be expected to eat less food) because animals ingesting saccharin consumed more total calories per day than animals given either intermittent or continuous access to sucrose. Intriguingly, rats are able to

monitor food intake in anticipation of sucrose access, but do not show the same effect when provided access to saccharin. More specifically, animals consumed less chow when a sweet-taste cue predicted access to sucrose-flavored yogurt, suggesting that they were regulating calorie intake over the entire session and therefore did not gain weight [50]. In contrast, a cue predicting access to saccharin-flavored yogurt increased food intake and led to greater weight gain, suggesting that artificial sweeteners were altering the homeostatic control of energy intake. In sum, artificial sweeteners may impair the ability to predict caloric intake by uncoupling signals related to sweet taste and calorie content [50, 51].

4. Behavioral and biological effects of artificial sweeteners

4.1 Rewarding effects

Animal studies support the idea that artificial sweeteners produce rewarding effects in that saccharin is self-administered by rats [67] and elicits binge-like intake in mice given limited daily access [26] or 2-day intermittent access [68] to a saccharin solution. Interestingly, increasing a no-access period to saccharin reinforces the bingeing behavior [30]. Saccharin also elicits ‘craving’ responses in rats, mimicking those produced by either sucrose or cocaine [67]. In these experiments, animals learn to self-administer cocaine, sucrose, or saccharin and then undergo 1 or 30 days of forced abstinence. When presented with a cue predicting access to the reinforcer, rats in the prolonged abstinent groups showed significantly higher seeking responses for all three commodities, reflecting a common phenomenon of ‘craving incubation’. Low calorie sweeteners, therefore, produce a similar pattern of reinstatement to those of natural reinforcers in an animal model of relapse. This suggests that artificial sweeteners may be poor substitutes for sugars as they could increase the risk of relapse in eating disorder patients.

On the other hand, the effect of artificial and natural sweeteners on reward-related behaviors in rats does not always overlap. For example, extended intermittent access to

sucrose blocks the reinforcing effect of sucrose in the conditioned place preference paradigm [28] and induces compulsive responding for sucrose in the conditioned suppression paradigm [18]. These effects were absent in groups given extended intermittent access to saccharin, although it should be noted that saccharin did not elicit binge behaviour in these experiments. Intriguingly, intermittent access to saccharin appears to increase sensitivity to develop a morphine conditioned place preference paradigm in male rats [28], suggesting that it may modulate the rewarding value of other reinforcers. Moreover, rats prefer saccharin over cocaine in a two-choice operant paradigm, an effect that is independent of prior drug experience [69].

4.2 Neural mechanisms

Artificial sweeteners provide little or no nutritive value, suggesting that consumption of these substances is driven, primarily, by their hedonic properties: these may be mediated by the same neural systems that underlie the rewarding properties of palatable food. In studying this assumption, Frank [70] reported that higher concentrations of both sucrose (up to 32%) and sucralose (concentrations matched to sucrose for sweetness) increased activation in the primary gustatory cortex of humans (frontal operculum and anterior insular), although sucrose activated additional regions implicated in feeding (e.g., midbrain, substantia nigra, and ventral striatum) [70]. The study also revealed differential functional connectivity associated with ingestion of the two substances, specifically recruitment of reward pathways for sucrose, but not sucralose.

Similarly, sucrose and low-calorie sweeteners both regulate the hypothalamic neuropeptide, orexin, although the two effects are not completely overlapping. For example, the selective orexin 1 receptor antagonist, SB-334867, blunts saccharin and sucrose drinking in mice [71, 72], and sucrose and saccharin bingeing decrease orexin mRNA in the lateral hypothalamus [73]. The latter is associated with reduced phosphorylated cyclic AMP

response binding protein (pCREB) in orexin neurons, at least in female rats [74]. This reduction was observed in melanin concentrating hormone (MCH) neurons but only following sucrose consumption, pointing to a potential dissociation of mechanisms mediating consumption of natural and artificial sweeteners. The fact that orexin processes are reduced in bingeing animals appears to contradict evidence that this neuropeptide reduces satiety and increases appetite [75]. The relationship between orexin levels and binge eating, however, likely involves a complex interaction with brain reward systems that could impact non-homeostatic eating. More specifically, orexin enhances dopamine levels in brain reward systems, so reduced orexin activity could reflect a hypodopaminergic state. Animals may compensate for this deficit by increased consumption of sucrose or saccharin in an attempt to maintain homeostatic levels of dopamine.

At the same time, there are subtle differences in the impact of dopamine manipulations on the intake of natural versus artificial sweeteners. Administration of either a D1 or D2 receptor antagonist (SCH23339 or raclopride) dose-dependently reduces sucrose, but not saccharin, intake [76] in a two-bottle choice paradigm. In addition, cues associated with either sucrose or saccharin presentation evoke dopamine release in the nucleus accumbens (NAcc) core, but the effect produced by sucrose-paired cues is much larger [77]. In line with this evidence, sucrose induces a larger DA release in the ventral striatum compared to saccharin [69]. A similar pattern of findings emerges regarding the relationship between feeding-related peptides and artificial versus natural sweeteners. Saccharin, like sucrose, increases mRNA levels of neuropeptide Y (NPY), orexin, and agouti related peptide (AgRP) [78, 79], changes that may underlie sweetener-induced increases in energy intake and weight gain. However, there is a distinct pattern of time-dependent changes following ingestion of the two commodities. More specifically, saccharin consumption leads to an immediate increase in NPY and orexin expression, whereas sucrose produces an immediate decrease in NPY and

AgRP that is followed by increased expression of these peptides within 10 minutes post-ingestion. Moreover, NPY infusions into the ventral tegmental area, NAcc, or lateral hypothalamus consistently increase sucrose consumption and/or the motivation to obtain sucrose [80]; in contrast, effects of these manipulations on saccharin intake are inconsistent [78, 81].

A separation of neural systems mediating the rewarding effects of sucrose and non-nutritive substitutes could be explained within the context of incentive sensitization. According to this theory [82], the ‘wanting’ component of reward depends on mesolimbic dopamine systems whereas ‘liking’ is mediated by opioidergic mechanisms. As noted previously, dopamine may have dissociable roles controlling responses to natural and artificial sweeteners, particularly in terms of cues predicting the presentation of one commodity of the other. There is some degree of overlap in the mediation of ‘liking’ natural and artificial sweeteners in that mice with deletion of the ion channel TRPM5 and TRPM4 taste receptors consume less of sucrose and saccharin than wild type mice [83], and mu opioid receptor knock out mice show reductions in both sucrose and saccharin bingeing [26]. Moreover, general opioid antagonism dose-dependently decreases palatable food bingeing [84], as well as saccharin preference and consumption [85]. On the other hand, mu opioid receptor knockout animals exhibit decreased licking of sucralose, compared to sucrose [86] and the mu opioid receptor agonist, DAMGO, selectively increases saccharin drinking in rats [87, 88]. Thus, although the neural substrates mediating hedonic responses to artificial and natural sweeteners share common elements, these are not completely overlapping.

5. Artificial sweeteners and sex differences

As with other basic biological processes, behavioral responses to palatable food often vary across sexes. Sex differences are attributed to a combination of chromosomal and hormonal differences between males and females, combined with gender constructs related to

societal expectations [89]. These help to explain sex differences in behavioral processes and the disproportional representation of one sex or the other in disorders or diseases. As an example, women transition more rapidly to compulsive drug use in addiction than males [90], and female rats exhibit enhanced escalation of heroin intake compared to male rats [91]. An increased rate of developing maladaptive drug use in females could reflect sex differences in dorsal striatal activity as this system controls the transition to compulsive drug use in addiction [92]. The effect may also be related to sexual dimorphism in brain reward systems, as these have been observed for dopamine D1 and D2 receptors in the frontal cortex and striatum of juvenile rats [93]. These findings fit with clinical evidence of differential activation of brain reward circuitry during craving in male and female patients with cocaine dependence [94].

Similar to drug reinforcers, sex differences emerge in male/female responses to palatable food. For example, women are more likely than men to exceed recommended limits on sugar intake [95] and to perceive sweet taste more intensely than men [96]. Female rats also show a higher preference than males of their species for both glucose and saccharin, an effect that is maintained even at the highest concentrations of saccharin [97]. Both males and females in this study preferred saccharin over glucose in conditions of short-term access; when access was extended, only males reverted to a higher preference for the natural sugar. These findings are reflected at the biological level with a higher proportion of female rats showing increased neuronal firing in the parabrachial pons in response to sucrose [98]. A similar profile of sex differences was observed in female and male rats provided with a saccharin solution, suggesting that the effect is driven by taste, not nutrient content [99]. Gonadal sex hormones likely contribute to these effects in that dopamine release in the NAcc shell is significantly increased when female rats are self-administering sucrose during the estrous phase of their cycle [100]. Finally, in choice paradigms, female rats are more likely

than their male counterparts to select sucrose over cocaine [101], suggesting that sweet solutions exert a more powerful control over behavior in this sex. Taken together, these data suggest that intake of palatable food is driven more strongly by hedonic properties, regardless of metabolic state, in females than males. It should not be surprising, therefore, that there is a higher proportion of female, compared to male, rats in binge-prone versus binge-resistant groups [102]. Sexual dimorphism in binge eating appears to extend to non-nutritive sweeteners as binge intake of saccharin is associated with increased chow intake in female, but not male, mice [26]. Although the data are preliminary, sex differences in reward processing related to palatable food may extend to artificial sweeteners.

6. Artificial sweeteners and substance use disorders

Binge intake of highly palatable food overlaps with many of the behavioral and biological features of drug abuse [15]. This suggests that BED and substance use disorder (SUD) may share a common etiology, although this contention remains controversial [103, 104].

Regardless of the interpretation, commonalities in maladaptive feeding and drug intake help to explain the high comorbidity between eating disorders and SUDs [6, 105]. Although it is difficult to untangle the causal relationship between the two, animal studies suggest that maladaptive eating precedes drug use in that rats that binge on fat later exhibit increased intake and motivation to consume alcohol [106]. Moreover, epidemiological studies in humans reveal that binge eating is associated, prospectively, with alcohol-related problems [107]. That is, individuals who met criteria for eating disorders were more likely to report negative consequences of alcohol use even if they did not drink more than non-eating disordered counterparts. Interestingly, the relationship between binge eating and drinking in a student population was stronger in males [108], which could explain the higher comorbidity of SUD with BED in men than women [109].

In humans who binge eat, intake of sweet foods is a significant predictor of the frequency of binge episodes [9]. Responses to sweet tastes, therefore, may play an important role in the emergence and acceleration of food or drug intake. This could explain why sucrose bingeing in rats alters subsequent responses to drugs, manifested as increased locomotor sensitization to psychostimulants, such as cocaine or amphetamine [110, 111]. There is some evidence that non-nutritive sweeteners produce similar effects. Rats bred for high saccharin intake show more rapid acquisition of cocaine self-administration, slower rates of extinction, and increased reinstatement to cocaine seeking [101]. The relationship could be bidirectional as rats bred for high intake of alcohol show increased saccharin consumption [112].

7. Conclusions

Binge eating is a common element of many eating disorders and one of the primary factors in growing rates of obesity. Both binge eating and obesity are driven by overconsumption of highly palatable food that is high in sugar and/or fat. This intake reflects hedonic, rather than metabolic, processing suggesting that sweet tasting food that contains minimal calories should help to reduce both binge eating and obesity. Neither clinical nor preclinical studies confirm this idea, although the data across experiments is often contradictory. Further work is required to unravel the relationship between behavioral and biological mechanisms mediating the rewarding effects of natural versus artificial sweeteners. Animal models are an important tool in this endeavor, particularly in terms of understanding sex differences in responses to palatable food.

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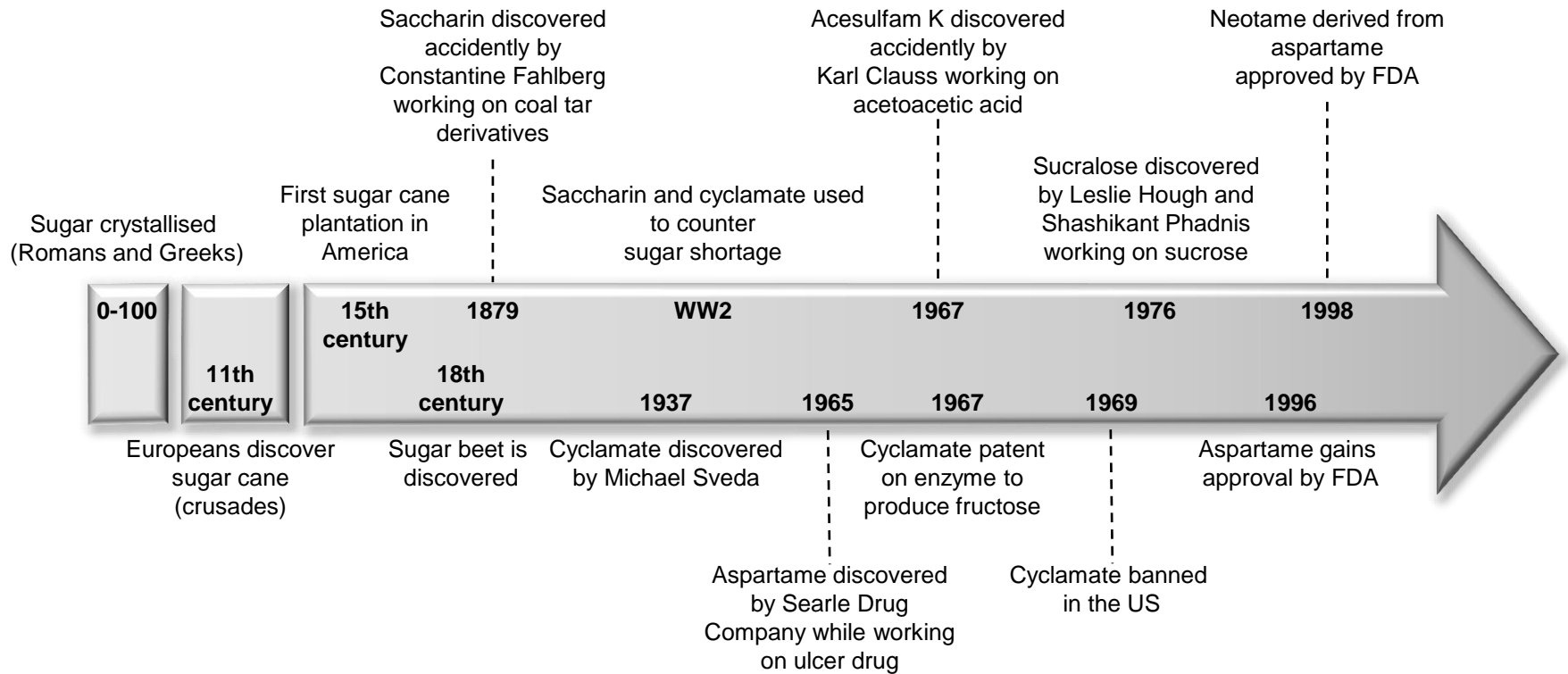
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Non-nutritive sweetener	Sweetening strength compared to sugar
Acesulfame Potassium	200x
Aspartame	200x
Cyclamate	40x
Neotame	8000x
Saccharin	300x
Sucralose	600x

Table 1 Relative sweetening strength of non-nutritive sweeteners

Note: In animal studies, the concentration of a sugar solution is usually 4% - 20%.