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Physiological mechanisms by which non-nutritive sweeteners may impact body weight and metabolism

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Abstract

Evidence linking sugar-sweetened beverage (SSB) consumption to weight gain and other negative health outcomes has prompted many individuals to resort to artificial, non-nutritive sugar (NNS) substitutes as a means of reducing SSB intake. However, there is a great deal of controversy regarding the biological consequences of NNS use, with accumulating evidence suggesting that NNS consumption may influence feeding and metabolism via a variety of peripheral and central mechanisms. Here we argue that NNSs are not physiologically inert compounds and consider the potential biological mechanisms by which NNS consumption may impact energy balance and metabolic function, including actions on oral and extra-oral sweet taste receptors, and effects on metabolic hormone secretion, cognitive processes (e.g. reward learning, memory, and taste perception), and gut microbiota.

Keywords

Non-nutritive sweeteners; Feeding; Obesity; Metabolism; Body weight; Taste perception; Energy balance; Sweetening agents; Gut; Brain

1. Introduction

Soft drinks and other sugar-sweetened beverages (SSBs) represent the largest source of added dietary sugars and discretionary calories for both children and adults in the United States [1]. SSB consumption is consistently identified as a major contributor to weight gain, obesity, type 2 diabetes and metabolic syndrome (for reviews, see [2–6]), and compelling evidence from large epidemiological studies and randomized controlled trials linking

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excessive sugar consumption to adverse health consequences has prompted leading healthcare professionals to recommend population-wide reductions in the intake of added sugars [7]. One approach to promote adherence to these recommendations is to substitute non-nutritive sweeteners (NNSs) for caloric sweeteners in foods and beverages. NNSs, also referred to as artificial sweeteners, non-caloric sweeteners, and high-intensity sweeteners, are highly potent sugar substitutes that permit reductions in the energy density of foods and beverages while maintaining high palatability. However, there is a great deal of controversy regarding the health consequences of NNS consumption. Numerous reviews and meta-analyses of epidemiological and experimental data have failed to reach a consensus on this matter, concluding that NNSs have potentially beneficial [8–10], harmful [11,12], or trivial [13,14] effects. Here we argue that NNSs are not inert compounds and we review potential physiological mechanisms by which NNS consumption may impact energy balance and metabolic function.

2. Oral Mechanisms

The sense of taste facilitates the detection of nutrients and toxins in potential food sources [15]. Carbohydrates are an essential energy source often equated with sweet taste, the detection of which reliably elicits acceptance responses across many species. Attraction to sweetness appears to have an innate basis; newborn mammals, including humans, respond positively to the presence of sweet taste in the mouth – even in the absence of prior experience – and will ingest, rather than reject the substance [16]. However, there is some evidence that these innate responses are susceptible to conditioning, and may be molded by pre- and post-natal experiences [16,17]. With the advent of NNSs, sweet taste is now frequently experienced in the absence of an energy source. What consequence, if any, does consumption of these engineered tastants have on the biology of taste?

2.1. Prandial orosensory stimulation

Perception of sweet taste is initiated in the oral cavity through the binding of a sweet tastant to a sweet taste receptor, a G-protein coupled receptor with two 7-transmembrane subunits T1R2/T1R3 [18]. Information from activated sweet taste receptor cells is conveyed to the brain via presynaptic cells which stimulate afferent cranial nerve fibers [15]. As with other signaling networks, this system can become saturated. Prolonged or repeated exposure to a taste stimulus can lead to an acute adaptation or a reduction in responsiveness and sensitivity to the stimulus. Adaptation in the taste system has been extensively documented [19–24]. This adaptation is mediated, at least in part, by physiological changes at the level of the taste receptor cell via receptor desensitization [25,26]. Repeated oral stimulation with natural, caloric sweeteners such as glucose and sucrose results in reduced responsiveness to, and perceived intensity of, both naturally and artificially sweet stimuli [20,25]. NNSs elicit the perception of sweet taste at low concentrations by binding with high affinity to one or more sites on the T1R2/T1R3 heterodimer [27–29]. This raises the possibility that prolonged or repeated receptor stimulation by high affinity NNSs may augment sensory adaptation and reduce sweet taste sensitivity, which may in turn influence the acceptability of caloric and non-caloric sweeteners. However, there are many outstanding questions. First, while cross-adaptation has been found to occur consistently when the adapting solution is a sugar,

studies have reported that NNSs, unlike their caloric counterparts, do *not* reliably produce cross-adaptation, and in some cases enhance the intensity of a sweet test stimulus, especially when the stimulus is caloric in nature [20,30]. Interpretation of such studies is complicated by the presence of a salient bitter component in many NNSs. In addition, previous studies have demonstrated that adaptation to certain compounds can induce particular taste qualities in water. Notably, Mcburney and Shick [31] and Bartoshuk [32] demonstrated that water acquires a sweet taste following adaptation to a bitter stimulus. This phenomenon may account for the sweetness enhancement effects following adaptation to NNSs. Particularly, adaptation to NNSs may produce a reduction in the sweetness of the test solution through cross-adaptation concomitant to an enhancement of sweet water taste which adds to the overall sweetness of the test solution [20,33]. It is also worth noting that NNSs are commonly consumed not in isolation but in mixtures with other sweetener types and/or with sour tastants such as citric acid. Nevertheless, NNS application to sweet taste receptor-expressing cells *in vitro* produces greater down-regulation of taste receptor subunits, suggesting that the magnitude of adaptation produced by sweet tastants may relate to relative binding affinity or differences in receptor site interactions [34]. Therefore, future work to characterize the effects of taste interactions and adaptation on taste sensitivity across a range of concentrations and NNS compounds at the molecular, cellular, and perceptual level is called for.

Second, the relationship between peripheral taste sensitivity, appetite, and intake is not fully understood (for review, see [35,36]), though some evidence suggests that prandial orosensory stimulation may contribute to the regulation of food intake. Studies have demonstrated that increased oral processing time (i.e., the length of time the food stimulus remains in the mouth) and increased orosensory exposure per unit of liquid or semisolid food consumption (i.e., sip or bite size) promotes satiation and decreases total intake [37–39]. Accordingly, Lavin et al. [40] reported differences in intake of a test lunch after chewing sucrose-containing pastilles over 10 min compared to consumption of the same sucrose amount consumed in liquid form over 2 min. However, these studies were not restricted to oral exposure and contributions of post-ingestive mechanisms cannot be ruled out. Indeed, studies comparing oral ingestion of nutrients to gastric infusion have demonstrated that oral administration generates a slower rate of gastric emptying, which may mediate reductions in appetite and intake [41,42]. In an effort to disentangle the effects of oral and post-ingestive mechanisms on intake, a recent study by Wijlens et al. [43] simultaneously but independently manipulated oral and gastric stimulation using a modified sham feeding (MSF) procedure. Compared to a no-stimulation control condition, oral exposure via MSF over 8 min – but not 1 min – paired with simultaneous gastric loads of 100 or 800 mL (infused at a constant rate of 100 mL/min) produced comparable reductions in *ad libitum* energy intake. Importantly, duration of oral exposure influenced the magnitude of suppression of energy intake, whereas gastric volume load did not. These findings suggest that orosensory stimulation may be at least as effective in suppressing intake as gastric volume. Nevertheless, whether the satiating effects of longer orosensory stimulation occur in the absence of post-ingestive stimulation remains unclear.

Studies employing modified sham feeding of sweetened solutions in the absence of post-ingestive stimulation have reported mixed effects on intake. Klein et al. found that sham intake of unsweetened and sucrose-sweetened flavored solutions increased as a function of sucrose concentration, suggesting that orosensory stimulation in the absence of post-ingestive feedback may enhance intake [44]. Similar effects were reported for sham intake of solutions sweetened with the NNS aspartame, with exaggerated effects observed in women with bulimia nervosa [45]. A tempting interpretation of these findings is that orosensory stimulation with sweeteners – independent of inhibitory post-ingestive nutrient stimulation – provokes greater intake. However, these studies are limited by small sample sizes and exclusion of male participants. Moreover, only sham intake of the solutions used for orosensory stimulation was measured in these studies. As such, extrapolation of these findings to real ingestion and to intake of other sweet tastants or nutrient classes should be performed with caution.

These studies highlight the need for further investigations of oral determinants of periprandial appetite and energy regulation as well as on the possible role of NNS consumption on altering these processes. In particular, more rigorous attempts to isolate contributions of orosensory mechanisms related to taste hedonics, gustatory sensitivity, and cephalic phase responses using both nutritive and non-nutritive sweet stimuli are called for.

2.2. Persistent alterations in taste perception

Many studies have interrogated the association between gustatory perception and obesity in humans with mixed results [46–52]. Several studies have reported a relationship between body mass index (BMI) and reduced suprathreshold sweet taste intensity perception [48,53], while others have found no such relationship [51,54]. Studies examining the relationship between sweet taste thresholds and body weight have reported lower thresholds in obese adolescents [49] but not in adult populations [46,51,55]. Interpretation of these conflicting findings is hindered by variations in the psychophysical approaches used to assess taste sensitivity, which limits inter-study comparisons [53]. Studies in rodents have demonstrated that high fat diet-induced obese (DIO) rats display higher sucrose preference and reduced lingual expression of the T1R3 subunit [56]. However, Chen et al. observed paradoxical effects, finding that reduced T1R3 expression in DIO rats was associated with a marked reduction in sweetener consumption and preference [57]. Notably, the latter study used the NNS saccharin, rather than caloric sucrose, to assess sweet taste preferences and consumption. Previous studies have demonstrated that rodents develop preferences for caloric sweeteners but not NNSs in the absence of oral taste signaling [58–60]. Thus, if high fat diet-induced reductions in lingual T1R3 expression lead to impaired taste sensitivity, preferences for caloric and non-caloric sweeteners might be impacted differently, as NNS preferences appear to depend upon oral taste signaling whereas caloric sweetener preferences are maintained in the absence of orosensory stimulation. However, taste sensitivity was not directly assessed in these studies, so it is unclear whether the observed changes in preference reflect an altered ability to detect sweeteners.

In contrast, Roux-en-Y gastric bypass (RYGB) reduces sucrose preference and intake in rodents and decreases sucrose taste detection thresholds in bypass patients [61]. The impact

of changes in taste sensitivity on weight loss or food intake following RYGB remains to be empirically determined [62], but it is possible that these alterations in taste perception may contribute to the procedure's clinical efficacy. However, there was no difference in hedonic ratings of sucrose solutions by gastric bypass patients pre- vs. post- surgery. This may be attributable to a lack of correspondence between sucrose detection thresholds and suprathreshold taste sensitivity. Alternatively, it is possible that the scaling procedure used to measure hedonic valuation of taste stimuli lacked the sensitivity to detect individual changes in sweetener acceptability [53].

With respect to NNSs, there is some evidence that consumption might produce persistent taste alterations. Mice pups exposed to the NNS acesulfame potassium (AceK) via maternal milk demonstrated increased preference thresholds for saccharin and sucrose in adulthood [63]. These behavioral changes were accompanied by alterations in the expression of proteins involved in taste signal transduction, including increased expression of T1R2 in the tongue and reduced expression of Gα-gustducin and leptin receptor Ob-Rb in the soft palate. These findings raise the possibility that excessive exposure to NNSs may produce alterations in taste transduction physiology. *In vitro* evidence supports this notion, though there is some discrepancy with regards to the directionality of effects. Ren et al. found that exposure of mouse hypothalamic cells to a hypoglycemic medium resulted in increased expression of the *Tas1r2* gene which encodes the T1R2 subunit of the sweet taste receptor, whereas exposure to higher concentrations of glucose produced the opposite effect [34]. The addition of sucralose into the medium produced an even more robust reduction in *Tas1R2* expression, with levels decreasing approximately 300% relative to baseline, raising the possibility that effect magnitude might be related to receptor affinity. Taken together, NNS exposure appears to produce some effect on taste receptor physiology in rodents, but the direction of these effects and their impact on taste sensitivity and preference cannot be determined on the basis of the limited evidence available. It is also important to consider that findings from rodent models investigating the relationship between sweet taste and preference may not translate to humans, as rodents appear to differ in their attraction to, and preference for, certain caloric and non-caloric sweeteners [64–66].

Whether NNS exposure alters taste perception in humans is unknown; however, there is some evidence to support this possibility. Neuroimaging studies have reported altered taste processing in heavy NNS users [67,68]. In particular, Small et al. reported an inverse association between NNS use and blood oxygen level dependent (BOLD) responses in the amygdala and insula in response to sucrose [68]. These findings have commonly been considered in the context of cue—reward associations (see below), but an alternative interpretation is plausible. BOLD responses in the amygdala and insula are also sensitive to taste intensity perception [69,70]. Thus, it is possible that altered activity in these regions in heavy NNS consumers reflects decreased afferent signaling and perceived intensity of sweet tastants.

3. Extra-oral Mechanisms

3.1. Extra-oral sweet taste receptors

Functional sweet taste receptors have also been identified in a variety of extra-oral tissues, including, but not limited to, the brain, pancreas, and gut. These receptors have been implicated in metabolic processes such as glucose sensing, secretion of satiety hormones, and glycemic control (for review see [71]). Intestinal enteroendocrine cells express a number of taste transduction molecules found in oral taste cells, including T1R2, T1R3 and Gα-gustducin [72]. Studies have shown that application of caloric sweeteners and NNSs to enteroendocrine cells *in vitro* can elicit secretion of incretin hormones glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide (GIP) from these cells *in vitro* via a T1R3-dependent mechanism [72,73]. Additionally, both natural sweeteners and NNSs increase expression and membrane trafficking of glucose transporters SGLT-1 and GLUT2 through their actions on intestinal sweet taste receptors [73,74].

However, there are conflicting data regarding the effects of NNSs on glucoregulation and gut hormone secretion *in vivo*. Several studies have shown that administration of NNSs increases SGLT-1- and GLUT2-dependent glucose absorption in mice (Margolskee et al., 2007b; Mace et al., 2007). In contrast, Fujita et al. failed to observe effects of acute NNS consumption in naïve rats on hormone secretion, reporting no effect of oral gavage of NNSs on incretin release or glycemic excursion in response to an intra-peritoneal glucose tolerance test (IPOGTT) in rats [75].

Investigations in humans have similarly yielded contradictory findings on this subject. Several studies have reported that oral consumption of an NNS-sweetened preload beverage increases GLP-1 in response to an OGTT in healthy subjects [76–78]. However, these studies reported discrepant effects on blood glucose. In a similar study in obese subjects, Pepino et al. found no effects of a sucralose preload on GLP-1 response to OGTT; however, increases in glucose, c-peptide, and insulin release as well as decreases in insulin clearance were observed [79]. Thus, there is a lack of consensus regarding glycemic effects of oral NNS consumption in humans. In contrast, studies employing intragastric or intraduodenal administration of NNSs have been remarkably unanimous in their findings, demonstrating no effect of NNSs on gut hormone secretion [80–82]. In an attempt to parse the contributions of oral and post-ingestive mechanisms, Ford et al. measured hormonal responses to oral or modified sham ingestion of a NNS preload and found that neither method of delivery produced changes in gut hormone secretion [83].

In summary, though data from *in vitro* studies strongly suggest that NNSs are physiologically active in the gut, *in vivo* studies in rodents and humans present conflicting evidence regarding the ability of NNSs to evoke post-ingestive responses. Unfortunately, the interpretation of these *in vivo* studies is hindered by marked methodological variations, including type of NNS employed, route of administration, duration of exposure, body weight status, and prior exposure to NNSs.

Sweet taste receptors have also been identified in several regions of the brain, including the hypothalamus, where they may be directly involved in glucose homeostasis. As mentioned

above, Ren et al. [34] reported that sweet taste receptor expression patterns in murine hypothalamic cells varied according to the glycemic index of the medium to which they were exposed, and sucralose exposure reduced the expression of *Tas1R2*. Recent evidence suggests that some NNSs may cross the blood brain barrier and interact with neurally-expressed sweet taste receptors *in vivo* [84]. It has been proposed that activation of these receptors by NNSs in nutrient-sensing brain regions may provide inaccurate feedback about extracellular glucose levels, which could in turn alter glucose homeostasis and intake [85].

3.2. Gut microbiota

The microbiome has been linked to multiple physiological roles, and growing evidence implicates gut microbiota in obesity and metabolic abnormalities [86]. The composition and function of the gut microbiota fluctuate between and within individuals and appear to be influenced by a variety of environmental factors, including diet [87–89]. Alterations in gut microbiota have been linked to obesity and type II diabetes [90–94]. These findings have fueled the proposition that interactions between diet and gut microbiota may promote a vulnerability to obesity and related metabolic disturbances. Studies dating back to 1980 have reported associations between NNS exposure and alterations in microbiomes or bacteria in culture [95–98], raising the possibility that NNSs might exert effects on human health via interactions with gut microbiota.

In support of this notion, a recent study by Suez et al. demonstrated that consumption of NNSs produces glucose intolerance via alterations to the gut microbiota [99]. In this study, commercial saccharin added to the drinking water of mice induced glucose intolerance in both lean and high-fat diet-fed (HFD) obese mice, and antibiotic treatment reversed these metabolic derangements. Transference of intestinal microbiota from NNS-consuming mice to controls replicated the glucose intolerance phenotype. Analysis of fecal microbiota composition revealed marked differences in microbial composition and function between saccharin-exposed mice and controls. In particular, saccharin consumption produced compositional alterations in bacterial taxa that have previously been linked to type II diabetes in humans, including *Bacteroides* and Clostridiales. Additionally, saccharin consumption was associated with enriched microbial metabolic pathways characteristic of enhanced energy harvest, a pattern that has previously been associated with obesity in mice. These findings were also recapitulated in humans. In a large sample of subjects, NNS consumption was correlated with clinical parameters of metabolic syndrome including body weight, fasting blood glucose, and impaired glucose tolerance. Gut bacterial populations in NNS consumers were distinct from non-consumers, and this was not accounted for by differences in BMI. Moreover, when placed on a regimen of controlled high saccharin intake, normal non-consumers of NNSs exhibited elevated blood glucose levels and altered gut microbiota composition after just 5–7 days. Transference of microbiota from these saccharin-exposed human subjects to lean NNS-naïve mice induced significant glucose intolerance, suggesting a causal role for saccharin-induced microbiota alterations. It should be noted, however, that these effects were observed in just four of seven participants. Moreover, the NNS regimen administered in both the rodent and human interventions represents the FDA's maximal acceptable daily intake of commercial saccharin – an amount that exceeds the average intake of sugar substitutes for even the heaviest users. As such,

these findings should be interpreted with caution until they can be replicated with a more ecologically relevant dose in a larger-scale, randomized controlled trial. Nevertheless, these findings introduce an unexpected and heretofore unexplored mechanism by which NNSs may produce detrimental metabolic consequences.

3.3. Uncoupling taste and post-ingestive consequences

An inability of NNSs to reliably elicit post-ingestive responses may not equate to physiological inertia. An alternative interpretation invoking the principles of classical Pavlovian conditioning postulates that repeated consumption of NNSs might disrupt energy regulation by degrading conditioned associations between sweet taste and its post-oral consequences [100]. Gustatory signals originating from foods are linked with post-ingestive metabolic consequences, thereby forging a conditioned association between orosensory cue and biological outcome. As a result of these learned associations, orosensory signals can guide ingestive behavior in an adaptive manner, promoting intake of foods associated with positive biological outcomes (e.g. energy absorption and utilization) and suppressing intake of foods associated with negative biological outcomes (e.g. malaise) [101]. These conditioned sensory cues can independently elicit a series of anticipatory pre-absorptive physiological responses – such as salivation and gastric acid secretion, secretion of metabolic hormones such as insulin, leptin, and ghrelin, and thermogenesis – referred to as cephalic phase responses (CPRs) [102]. CPRs serve to facilitate digestion, absorption, and metabolism [103], and may also dynamically modulate appetite and satiety in a manner that serves to protect homeostasis [104]. In natural settings, sweet taste reliably predicts the presence of carbohydrates that serve as an energy source. By virtue of this association, sweet tastes in the mouth would be expected to elicit CPRs that signal and prepare for the impending arrival of carbohydrates in the gut, and the available body of evidence strongly supports this suggestion (for review, see [103]). When a conditioned stimulus (CS) is repeatedly presented in the absence of the unconditioned stimulus (US), it loses its predictive value and its ability to elicit the conditioned response. Based on this principle, it has been suggested that repeated experience with NNSs, which provide the conditioned orosensory stimulus of sweet taste in the absence of post-ingestive nutritive consequences, might lead to a suppression of conditioned CPRs [105]. Further, this suppression may persist even when sweet taste is once again accompanied by caloric content due to a devaluation of the CS [106]. This CS-US decoupling could impair the ability of sweet taste to predict energy availability and appropriately guide intake.

Supporting evidence for this hypothesis was obtained in rodents exposed to inconsistent pairings of sweet taste and calories. Rats with a history of exposure to NNS-sweetened foods and liquids showed increased weight gain, energy intake, and adiposity compared to control rats exposed to similar diets sweetened with glucose, for whom sweet taste consistently matched caloric content [107,108]. Moreover, NNS-exposed rats displayed an impaired ability to compensate for additional calories consumed in a novel, calorically-sweetened pre-meal by reducing intake at subsequent feeding opportunities, and also demonstrated blunted thermic responses to caloric sweet meals [107]. A similar study corroborated the effects of NNS exposure on body weight and energy intake, and further demonstrated that, compared to glucose-exposed controls, NNS-exposed rats displayed increased blood glucose and

decreased GLP-1 in response to an OGTT [109]. Consistent with the notion that NNS experience interferes with ability of sweet orosensory cues to elicit CPRs, these glycemic impairments were not observed when glucose was administered by intragastric gavage, bypassing the oral cavity. Taken together, these data support the notion that NNS consumption may disrupt energy homeostasis by interfering with the predictive relationship between sweet taste and post-ingestive outcomes. It is important to note that these findings contradict earlier work by Berthoud et al. [110], who found that ingestion of a saccharin solution reliably elicits a rapid cephalic phase insulin response (CPIR) in rats which was not easily extinguished, suggesting that this response may possess an unconditioned component. However, CPIR was measured over only 10 trials in this study, which may be insufficient to produce extinction.

3.4. Uncoupling taste and reward

Whether prolonged NNS exposure alters physiological responses to caloric sweeteners in humans remains unclear. However, neuroimaging studies have provided some evidence that NNS consumption may alter the relationship between sweet taste and reward. Frank et al. found that tasting sucrose and sucralose activated common taste pathways, but absolute brain response after sucrose was stronger than for sucralose [111]. Furthermore, sucrose – but not sucralose – recruited strong connectivity between primary taste pathways and midbrain reward circuits in relation to behavioral pleasantness ratings. These findings were confirmed by Smeets et al., who reported that striatal activation was greater in response to a naturally sweetened solution, whereas NNSs produced greater amygdala activation [112]. These data suggest that the brain is capable of distinguishing between caloric sweeteners and NNSs even though both are perceived as similarly sweet. This might be related to post-ingestive responses associated with caloric vs. non-caloric sweeteners. Alternatively, it may reflect differences in taste profile between NNSs and natural sweeteners. Though these studies controlled the perceived sweetness intensity of the two stimuli, they did not assess whether subjects were able to discriminate between the two sweetener types on the basis of other taste characteristics. Thus, this possibility cannot be excluded.

Recent studies have reported altered processing of caloric and non-caloric sweet taste stimuli in habitual NNS consumers. A study by Green and Murphy revealed that sweet taste elicited greater activation of reward-related brain regions in self-reported diet soda drinkers compared to non-diet soda drinkers, and that habitual diet soda drinkers did not demonstrate differential brain responses to nutritive and NNSs [67]. These results suggest that regular NNS consumption may be associated with changes in the reward experienced from caloric and non-caloric sweeteners. Further, Rudenga and Small reported that frequency of NNS use is negatively associated with brain response to sucrose in the amygdala and insula [68]. The amygdala is critically involved in flavor-nutrient conditioning in rodents [113–115], and in the central representation of the reward value of sensory-predictive cues [116]. The amygdala is also activated to a greater extent by sensory cues that predict the immediate arrival of caloric vs. non-caloric solutions [117]. The insula has also been implicated in integrating orosensory and homeostatic signals [118], and was found to interact more strongly with feeding-related regions such as the hypothalamus and striatum in response to nutritive as opposed to non-nutritive taste stimuli [119]. Based on these observations, it

might be speculated that blunted amygdala and insula response to sucrose in habitual NNS consumers may reflect a reduction in the predictive value of sucrose and a decoupling of sensory cue from reward, though future work in which NNS exposure is manipulated experimentally is needed to bolster this interpretation.

Contrary to these findings, a recent clinical trial reported that repeated consumption of NNS- and sucrose-sweetened versions of a drink did not alter the reward value of either version [120]. In this study, subjects consumed fixed portions of sucrose- and NNS-sweetened versions of a beverage that were distinguishable by means of colored labels. Each version was offered 10 times in semi-random order over a 20-day conditioning period. Before and after this conditioning phase, the reward value of each drink was assessed using behavioral tasks measuring implicit and explicit wanting, liking, and expected satiety. Additionally, BOLD response to NNS- and sucrose-sweetened liquids was measured before and after conditioning. Outcomes of both behavioral tasks and fMRI data indicated that conditioning with repeated exposures did not affect the reward value of either version of the drink. These findings suggest that the learned relationships between sweet taste and reward might be relatively resistant to extinction, though it is possible that the limited exposure to NNS in this study was insufficient to degrade conditioned associations that developed over a lifetime.

3.5. Cognitive influences

In humans, beliefs and expectations about the caloric content of a food or beverage may influence brain function and metabolism. For example, consuming the same milkshake produces greater decreases in circulating ghrelin when participants believe that it is “indulgent” as opposed to “sensible” [121]. Likewise, a flavored beverage produces greater hypothalamic response when preceded by the label “treat” compared to the label “healthful”, with the overall pattern of brain activation associated with the treat label more closely resembling response to a prototypical treat (milkshake) [122]. There is also evidence that consuming food believed to be low in calorie content can produce reduced satiety and lead to “rebound” eating [123,124], though not all studies support such an effect [125,126]. These findings raise the possibility that NNSs might influence intake and metabolism simply by creating the impression that a food or beverage is less caloric than its actual energy content.

A second way in which NNS may impact cognition is by passing through the blood brain barrier to produce deleterious effects on brain tissue. In a recent study, Cong et al. [84] demonstrated that orally ingested AceK is able to cross the mouse blood brain barrier and accumulate in brain tissue. Chronic consumption (40 weeks) of this NNS produced neurosynaptic- and metabolism-related genomic and proteomic abnormalities in the hippocampus, including reduced protein expression of the T1R3 subunit and the glucose transporter Glut1, functional ATP depletion, and dysregulation of proteins involved in cell growth and survival. They further demonstrated that the chronically exposed animals showed signs of impaired hippocampal-dependent learning, as assessed with the Morris Water Maze. AceK-treated T1R3 knockout mice failed to exhibit these cognitive impairments, suggesting an integral role for the T1R3 subunit. It should be noted that while

the doses of AceK employed in this study were within the acceptable daily intake range for AceK set by the FDA, daily AceK intake by the experimental animals was likely higher than what most humans experience on average. Moreover, AceK may be unique among NNSs in its ability to cross the blood brain barrier, as there is no evidence that other NNSs accumulate in the blood or are absorbed from the intestine. Thus, the epidemiological relevance of these findings may be limited to suprathreshold levels of intake of AceK.

Nevertheless, the possibility that some NNSs might cross the blood brain barrier to produce hippocampal damage may be relevant for consideration of the role of NNSs in energy balance and metabolism. The hippocampus is sensitive to satiety signals in humans and animals [127,128], and there is a strong body of evidence demonstrating detrimental effects of high fat and high sugar diets on hippocampal function. Excess consumption of high fructose corn syrup, and to a lesser extent, sucrose, impaired hippocampal-dependent spatial learning and memory in rats [129]. Chronic exposure to a high-fat and refined sugar (HFS) diet has also been shown to reduce hippocampal levels of brain-derived neurotrophic factor, synaptic plasticity, and spatial learning performance in rodents [130]. In humans, self-reported (HFS) diet is associated with poorer performance on hippocampal-dependent memory tasks, as well as reduced accuracy in tracking prior food intake and diminished sensitivity to interoceptive hunger and satiety signals [131].

There is also evidence that hippocampal dysfunction may promote weight gain. Rats with neurotoxic lesions of the hippocampus exhibit excessive *ad libitum* feeding and weight gain [132]. Additionally, hippocampal lesions impaired the ability of rats to use interoceptive cues arising from 0 and 24 h food deprivation as discriminative signals [133]. In particular, lesioned rats exhibited increased appetitive responding in the presence of energy state cues that signaled non-reinforcement, whereas responding to reinforced cues remained intact. These data suggest that impaired discriminative responding following hippocampal lesions results from an inability to inhibit activation of the memory of food reinforcement. As a consequence, satiety cues may be less able to suppress the ability of food-related cues to evoke the memory of food reinforcement and excite appetitive and consummatory behavior [133–135]. Taken together, these data suggest that dietary factors such as excess consumption of fats, refined sugars, and perhaps also of certain NNSs that cross the blood brain barrier and disrupt hippocampal function may impair sensitivity to interoceptive signals, dysregulate appetitive behavior, and thereby promote food intake.

4. Conclusions

The addition of NNSs to foods and beverages has become increasingly pervasive in the modern food environment. Although the existing literature on the biological consequences of NNSs, particularly in humans, remains highly controversial, amassing evidence suggests that NNSs are not physiologically inert, and may influence feeding and metabolism through a variety of peripheral and central mechanisms. The determinants of energy homeostasis and ingestive behavior are exceptionally diverse and complex. Contributions of oral, gastrointestinal, endocrine, and neural mechanisms, and the manner in which these systems interact to regulate energy balance, remain insufficiently understood. Conclusions about the impact of NNSs on human health are made within the context of the level of current

understanding. As understanding advances so too should the consideration of the impact of NNS use on human health.

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Highlights

- The health consequences of non-nutritive sweetener (NNS) use are controversial.
- Evidence suggests NNSs may impact energy balance and metabolic function.
- We review the evidence for central and peripheral physiological effects of NNSs.
- Limitations of the current literature base and health implications are discussed.