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NUTRITION AND THE BRAIN (J NASSER, SECTION EDITOR)

Effects of Non-nutritive Sweeteners on Sweet Taste Processing and Neuroendocrine Regulation of Eating Behavior

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Abstract

Purpose of Review Non-nutritive sweeteners (NNS) are increasingly used as a replacement for nutritive sugars as means to quench the desire for "sweets" while contributing few or no dietary calories. However, there is concern that NNS may uncouple the evolved relationship between sweet taste and post-ingestive neuroendocrine signaling. In this review, we examine the effects of NNS exposure on neural and peripheral systems in humans.

Recent Findings NNS exposure during early development may influence sweet taste preferences, and NNS consumption might increase motivation for sweet foods. Neuroimaging studies provide evidence that NNS elicit differential neuronal responsivity in areas related to reward and satiation, compared with caloric sweeteners. Findings are heterogenous regarding whether NNS affect physiological responses.

Summary Additional studies are warranted regarding the consequences of NNS on metabolic outcomes and neuroendocrine pathways. Given the widespread popularity of NNS, future studies are essential to establish their role in long-term health.

Keywords Non-nutritive sweeteners · Low-calorie sweeteners · Sweeteners · Artificial sweeteners · Sweet taste · Hormones · Obesity · Insulin · Incretins · GLP-1 · Brain · fMRI · Neuroimaging · Obesity · Reward · Satiety · Food intake · Feeding behavior · Appetite · Hypothalamus · Striatum · Insula · Amygdala

Introduction

A growing body of evidence has linked increased caloric sugar consumption with obesity risk [1–3]. Accordingly, non-nutritive sweeteners (NNS) have become a popular alternative for added sugar intake, satisfying the craving for "sweets" while providing few or no calories. NNS use is rapidly increasing; currently, over 40% of US adults and 25% of adolescents and children are habitual NNS consumers [4]. Notably, among American children and adolescents, NNS intake has increased by 200% since 1999 [4]. Furthermore, given the widespread distribution of NNS in drinks and foods, consumers are often unaware that they are even ingesting NNS [5, 6]. Despite the increasing usage of NNS, and NNS being largely marketed as strategic tools for weight management, the prevalence of obesity and associated metabolic disorders has not decreased; rather, rates of the co-epidemics of obesity and type 2 diabetes (T2DM) have continued to rise over the past several decades [7, 8]. Notably, a recent advisory from the American Heart Association recommended against prolonged consumption of NNS beverages by children, while also concluding that NNS beverages could potentially be a useful replacement strategy for adult chronic high consumers of sugar-sweetened beverages [9]. In addition, while epidemiological evidence suggests that NNS exposure throughout the lifespan (and as early as in utero) can contribute to risk for weight gain [10–13] and risk for metabolic derangements, including type 2 diabetes [14], other studies using experimental designs have reported that NNS have neutral or beneficial effects regarding body weight [15–18] and glucose metabolism [19]. Given the equivocal evidence regarding the efficacy of NNS, and the paradoxical increase in prevalence of both NNS use and metabolic disorders, it is imperative that the

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potential neural and peripheral implications of NNS consumption throughout the lifespan are understood (Fig. 1). The purpose of this article is to review and summarize the current literature, and to address the gaps in knowledge regarding the effects of both acute and chronic NNS exposure across the lifespan on glucose metabolism, sweet taste perception and preference, and neural systems involved in appetite and reward, with an emphasis on findings from human studies.

NNS and Sweet Taste

While caloric sugars and NNS have varying chemical structures, they all interact with the heterodimeric sweet taste receptor complex, T1R2/T1R3 [20]. Notably, sweet taste perception plays a role in carbohydrate metabolism and reward [21], and sweet taste preference has been linked to the likelihood of children becoming overweight or obese [22]. Additionally, sweet-liking is predictive of weight gain over time in some adult populations [23, 24]. Given the potential metabolic consequences of heightened hedonic liking for sweet, it is important that the possible influences of NNS on taste perception and preference are well understood.

A growing body of evidence in rodents, and a limited number of studies in humans, suggests that NNS exposure or consumption during early development may influence sweet taste processing. The formation of taste preferences, including preference for sweet, begins before birth; both rodent and human studies have demonstrated that maternal diets during pregnancy and lactation, in addition to the offspring's diet during the first months of life, influence flavor learning, conditioning, and acceptance [25–27]. The effects of in utero and early-life exposure to NNS on offspring sweet taste learning, perception, and preference have in large part been elucidated by rodent studies. Rosales-Gomez et al. recently reported that young mice who habitually consumed oral sucralose directly after weaning had heightened preference for sweetened water and increased weight gain at approximately 15 weeks of life [28]. Other rodent studies have addressed how in utero and lactational NNS exposure influences offspring taste preference. Mouse pups exposed to acesulfame potassium (aceK) prenatally and during lactation via maternal diet exhibit greater sweet taste preference in adulthood compared with control

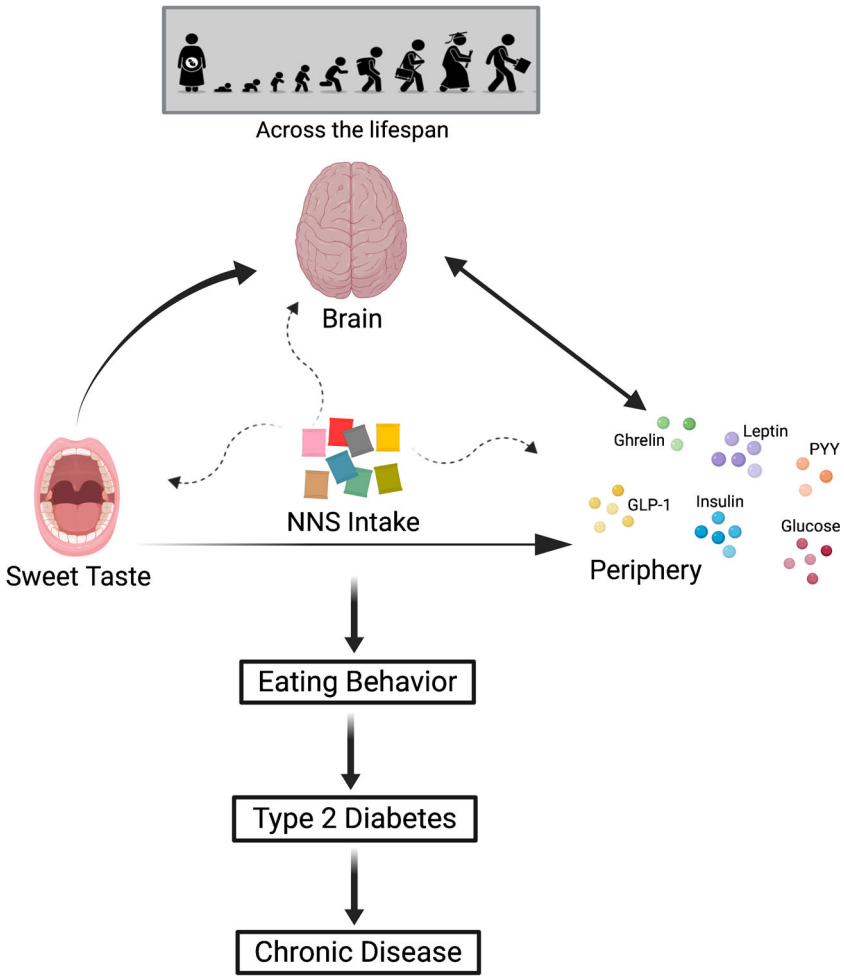

Fig. 1 Downstream potential effects of NNS intake on neuroendocrine systems involved in appetite regulation and eating behavior. The taste of a sweet substance activates sweet taste receptors, including in the oral cavity and brain. Exposure to NNS, which uncouple sweet taste and energy content, may dysregulate sweet taste signaling pathways and affect brain and metabolic processes across the lifespan, which, in turn, may contribute to altered eating behavior, T2DM, and chronic disease. Figure created with BioRender

mice [29, 30], and furthermore, infusion of aceK during the early postnatal stage promoted unfavorable gustatory system changes in young mice [31].

Together, these findings in animal models have particular clinical implications for pediatric populations. NNS are frequently ingested by nursing infants; it has been shown that saccharin, sucralose, and aceK were present in 65% of breast milk samples from twenty lactating mothers, independent of the mothers' NNS dietary intake [32]. However, the specific magnitude and prevalence of fetal NNS exposure in humans remains unknown [33•]. Studies in children examining the effects of habitual NNS consumption on dietary preference for sweet foods are limited to cross-sectional analyses. A study among UK children and adolescents (ages 4–18) found that boys who reported any dietary consumption of artificially sweetened beverage(s) (ASBs) had higher dietary intake of sugar from solid foods when compared with boys who reported consuming only sugar-sweetened beverages (SSBs) or those who were non-consumers of either SSBs or ASBs [34]. However, the majority of this cohort consumed both SSBs and ASBs (43%), while a subset of 18% consumed only ASBs [34]. More recently, Sylvetsky et al. reported the first results from a US study that used 2011–2016 National Health and Nutrition Examination Survey (NHANES) data to examine associations between NNS beverage consumption and dietary intake in children and adolescents. They found that consumers of low-calorie sweetened beverages, whether consumed alone or in conjunction with SSBs, displayed higher energy, carbohydrate, total sugar, and added sugar intake compared with children and adolescents who were classified as only water consumers [35••]. In a separate study that used NHANES data, Sylvetsky and colleagues also demonstrated positive associations between dietary NNS consumption and obesity in adolescents [36]. It should be noted that the NHANES data were limited to self-reported dietary intake, based on only a single or two-day recall, and that given the cross-sectional nature of the studies, confounding by reverse causation is possible. Nevertheless, the findings from Sylvetsky et al. are consistent with one of the proposed mechanisms by which early-life NNS exposure may impact future body composition via dysregulation of the developmental programming of taste preferences. Chronic NNS consumption may uncouple the functionality of sweet taste to signal the post-ingestive caloric consequences of eating sweet foods, in turn, enhancing sugar intake [37–41]. Taken together, further studies examining the effects of early-life NNS exposure on taste preference, dietary intake, and body weight regulation are warranted. Future areas of study include replication of findings in animal models and studies that include more rigorous experimental methods in humans.

Few human studies have addressed how NNS consumption influences sweet taste preferences in adulthood. A study by Casperson et al. aimed to determine the effects of consuming a SSB or NNS beverage on the reinforcing value of sweet foods. Young adults ingested either acute oral sucralose (Splenda®) or sucrose, matched for sweetness and pleasantness, with a standardized meal. Consumption of sucralose, but not sucrose, heightened the motivation to gain access to sweet foods post meal [42•]. Sucralose increased the relative reinforcing values of sweet snacks, compared with salty or savory snacks, suggesting that acute NNS consumption might alter desire for sweet foods and eating behavior [42•]. In contrast, a recent industry-funded study reported that among French adults, water and low-calorie sweetened (LCS) beverage ingestion did not have differential effects on the selection of, or motivational ratings towards, sweet foods [43]. Furthermore, appetite for sweet foods was neither affected by acute nor longer-term exposure to the LCS beverage [43]. It is important to note that the respective experimental studies by Casperson et al. and Fantino et al. utilized different NNS methodologies, the latter employing a LCS lemonade that included several NNS (aceK, aspartame, and sucralose) in combination with other compounds. Hill and colleagues examined the acute effects of consuming a SSB (Sprite®), a NNS beverage (Sprite Zero®), or an unsweetened beverage (carbonated water), in combination with a standardized meal, on subsequent product choice and subjective responses to a sugar-sweetened food among young adults. They found that participants who consumed the NNS drink, relative to those who had consumed the SSB or water, were more likely to choose a high calorie food item (specifically, candy) during a food product choice task, compared to other food options [44]. In addition, participants who consumed the NNS beverage felt less satisfied after eating a sugar-sweetened snack (cookies), compared with subjects who consumed the SSB or water [44]. Taken together, these studies provide equivocal evidence for the impact of NNS consumption on adult sweet taste preference and eating behavior, and future experimental studies are warranted.

NNS and Metabolic Hormones

There has been much debate regarding whether NNS have effects on metabolic hormones. In vitro studies showed that NNS bind with high affinity to the T1R3 subunit of the sweet taste receptor complex, which is expressed on the tongue and throughout the digestive tract [45–47], and that NNS stimulate incretin and insulin release in both the enteroendocrine cells in the gut as well as beta cells in the pancreas [20, 48–52]. While evidence from in vitro studies has been compelling, in vivo studies testing the effects of NNS on metabolic hormone secretion have produced mixed results. Studies in rodent models have been reviewed elsewhere [53], and in this review, we highlight human studies that have examined the effects of NNS on metabolic hormones (Table 1).

Table 1 Summary of findings from human studies examining NNS effect on hormone levels, specifically insulin, glucagon like peptide 1 (GLP-1), peptide YY (PYY), gastric inhibitory polypeptide (GIP), leptin, ghrelin, and glucagon

Author	Year	Age Group/ Size	Participant Characteristics	NNS Used	Dosage and Method of Delivery	Insulin	C-peptide	GLP-1	PYY	GIP	Leptin	Ghrelin	Glucagon
Abdallah et al.	1997	12 Male Adults	Lean	Aspartame	18mg aspartame, tasted	Decreased	n/a	n/a	n/a	n/a	n/a	n/a	No effect
Ahmad et al.	2019	17 Adults (10F)	Lean	Aspartame, Sucralose	425mg aspartame, 136mg sucralose, ingested for 2 weeks	No effect	n/a	No effect	n/a	n/a	No effect	n/a	n/a
Anton et al.	2010	31 Adults	19 Lean, 12 Obese	Stevia, Aspartame, Sucrose	400g preload meal with stevia, aspartame or sucrose	Lower with stevia and aspartame than sucrose	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Argyri et al.	2013	70 Adults (28F)	T2DM	Diabetic dessert	Not specified, ingested	No effect	No effect	n/a	n/a	n/a	n/a	n/a	n/a
Bonnet et al.	2018	50 Adults (28F)	28 Lean, 22 Overweight	Aspartame+ aceK	129mg aspartame + 13mg aceK for 12 weeks, 4 week washout, then 258 mg aspartame + 26mg aceK for 12 weeks	No effect	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Brown, R et al.	2009	22 Adolescents and Young Adults (12F)	Overweight	Sucralose+ aceK	68mg sucralose + 41mg aceK (Diet Rite Cola), then OGTT	No effect	n/a	Increased	n/a	n/a	n/a	n/a	n/a
Brown, R et al.	2012	44 Adolescents and Young Adults (27F)	25 Overweight (Nondiabetic), 9 T1DM lean, 10 T2DM obese	Sucralose+ aceK	68mg sucralose + 41mg aceK (Diet Rite Cola), then OGTT	n/a	No effect	Increased in T1DM and nondiabetic overweight groups, not T2DM group	No effect	n/a	n/a	n/a	n/a
Brown, A et al.	2011	8 Female Adults	Lean	Sucralose	42mg sucralose drink, 42mg sucralose + 50g sucrose drink, then standard meal	No effect	n/a	n/a	n/a	n/a	n/a	No effect	No effect
Dhillon et al.	2017	64 Adults (41F)	Obese	Sucralose	Not specified, in solid and liquid form; taste vs. ingestion	Early rise higher with taste of solid	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Ford et al.	2011	8 Adults (7F)	Lean	Sucralose	2mmol/L in water, or 2mmol/L in water with maltodextrin, tasted and ingested	No effect	n/a	No effect	No effect	n/a	n/a	n/a	n/a
Grotz et al.	2003	128 Adults (42F)	Obese	Sucralose	667mg sucralose, via ingested capsule, 13 week exposure	n/a	No effect	n/a	n/a	n/a	n/a	n/a	n/a
Grotz et al.	2017		Lean	Sucralose		No effect	No effect	n/a	n/a	n/a	n/a	n/a	n/a

Table 1 (continued)

Author	Year	Age Group/ Size	Participant Characteristics	NNS Used	Dosage and Method of Delivery	Insulin	C-peptide	GLP-1	PYY	GIP	Leptin	Ghrelin	Glucagon
		47 Male Adults			667mg sucralose, via ingested capsule, 12 week exposure								
Higgins and Mattes	2019	154 Adults (87F)	85 Overweight, 69 Obese	Saccharin, Aspartame, Stevia, Sucralose	73mg saccharin, 58mg aspartame, 66mg stevia, 16mg sucralose, via drink, 12 week exposure	No effect	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Higgins et al.	2018	100 Adults (50F)	Lean	Aspartame	0, 350, 1050mg aspartame, via drink, 12 week exposure	No effect	n/a	No effect	n/a	No effect	No effect	n/a	n/a
Lertrit et al.	2018	15 Adults (11F)	8 Lean, 1 Overweight, 6 Obese	Sucralose	200mg sucralose, via capsule, 4 week exposure	Decreased	n/a	Increased	n/a	n/a	n/a	n/a	n/a
Ma et al.	2009	7 Adults	Lean	Sucralose	80mg sucralose, 800mg sucralose, via NG tube	No effect	n/a	No effect	n/a	No effect	n/a	n/a	n/a
Ma et al.	2010	10 Adults (2F)	Lean	Sucralose	960mg sucralose, via NG tube	n/a	n/a	No effect	n/a	n/a	n/a	n/a	n/a
Nichol et al.	2019	21 Adults (17F)	10 Lean, 11 Obese	Sucralose	48mg sucralose, taste vs. ingestion then OGTT	Increased in taste vs. ingestion for both weight groups, late increase in obese group during OGTT	No effect	n/a	n/a	No effect	n/a	n/a	n/a
Overduin et al.	2016	20 Adults (10F)	10 Lean, 10 Obese	Erythritol+ Sucralose	8g erythritol, 4mg sucralose in drink and meal, compared to sucrose control	No effect	n/a	Increased compared to sucrose	Increased compared to sucrose	n/a	n/a	n/a	n/a
Pepino et al.	2013	17 Adults (15F)	Obese	Sucralose	48mg sucralose, ingested, followed by OGTT	Increased	Increased	No effect	n/a	No effect	n/a	n/a	No effect
Romo-Romo et al.	2018	66 Adults (49F)	Lean	Sucralose	12mg sucralose consumed 3x/day, via drink, 14 day exposure	Decreased insulin sensitivity, increased acute insulin response	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Sakurai et al.	2012	21 Male Adults	Lean	Sucralose, aceK, Aspartame, Erythritol	Not specified, mixed with 5mg sucrose via drink, co-ingested with a meal	n/a	n/a	No effect	n/a	n/a	n/a	n/a	n/a

Table 1 (continued)

Author	Year	Age Group/ Size	Participant Characteristics	NNS Used	Dosage and Method of Delivery	Insulin	C-peptide	GLP-1	PYY	GIP	Leptin	Ghrelin	Glucagon
Steinert et al.	2011	12 Adults (6F)	Lean	Sucralose, Aspartame, aceK	169mg aspartame, 220mg aceK, 62mg sucralose, via NG tube	No effect	n/a	No effect	No effect	n/a	n/a	No effect	n/a
Sylvetsky et al.	2016	61 Adults (34F)	Overweight	Sucralose, Sucralose+aceK	Experiment 1: 68mg, 170mg and 250mg sucralose; Experiment 2: Diet Rite Cola: 68mg sucralose + 41mg aceK; Diet Mountain Dew: 18mg sucralose, 18mg aceK, 57mg aspartame; 68mg sucralose + 41mg aceK dissolved in seltzer water, all preloads to OGTT	No effect	No effect	Increased after sucralose + aceK, Diet Rite Cola, and Diet Mountain Dew; no effect of sucralose alone	n/a	No effect	n/a	n/a	n/a
Temizkhan et al.	2015	16 Adults (8F)	8 Obese, 8 Obese T2DM	Aspartame, Sucralose	72mg aspartame, 24mg sucralose, ingested, then OGTT	No effect	No effect	Increased after sucralose	n/a	n/a	n/a	n/a	n/a
Tey et al.	2017	30 Male Adults	Lean	Aspartame, Monk fruit, Stevia	440mg aspartame, 630mg monk fruit, 330mg stevia, via drink, prior to test meal, sucrose as a positive control	Increased acutely after test meal, no difference in AUC	n/a	n/a	n/a	n/a	n/a	n/a	n/a
Wu et al.	2012	10 Adults (3F)	Overweight	Sucralose	60mg sucralose drink, followed by test meal	No effect	n/a	No effect	n/a	No effect	n/a	n/a	n/a
Wu et al.	2013	10 Male Adults	Overweight	Sucralose, aceK, Sucralose+aceK	52mg sucralose, 200mg aceK, 46mg sucralose + 26mg aceK, then OGTT	No effect	n/a	No effect	n/a	n/a	n/a	n/a	n/a

The effects of acute ingestion of NNS on incretin and insulin responses have been studied using a variety of delivery methods as well as different dosages and types of NNS [54–66]. Interestingly, Diet Rite Cola®, which contains sucralose and aceK, among other colorants and preservatives, was found to increase GLP-1 secretion when compared with a water or a seltzer control when consumed prior to an oral glucose tolerance test (OGTT) in overweight and obese individuals [54–56]. However, studies examining the effects of NNS dissolved solely in water have been mixed, with the majority showing no effect of acute NNS consumption on hormone secretion [56, 57, 59, 64]. While Temizkhan et al. observed an increase in GLP-1 levels when sucralose vs. water was consumed prior to glucose ingestion, these effects were not observed with an aspartame preload [57]. Sylvetsky and colleagues found no significant difference between varying concentrations of sucralose dissolved in water compared with water alone when consumed prior to an oral glucose load on peripheral insulin, glucose, C-peptide, or GLP-1 levels in overweight individuals [56•]. Likewise, Ford and colleagues found no difference between sucralose compared with water preloads on insulin or GLP-1 responses to oral glucose [64]. Additionally, Wu and colleagues found no effect of sucralose or aceK, when consumed alone or in combination, on peripheral insulin or GLP-1 concentrations before or during an OGTT [59]. Future work is needed to determine if some of the observed NNS effects on peripheral GLP-1 are attributable to the colorants or preservative present in diet soda given that the majority of studies that found an effect on GLP-1 secretion utilized Diet Rite Cola®.

The studies mentioned above utilized acute glucose ingestion as a caloric load, whereas other studies used a standardized meal to examine the effects of NNS consumption on hormone responses in a more "real-life" scenario. These studies have largely found no effects of acute NNS ingestion on hormone responses to standardized meals [60, 65, 67, 68]. Wu and colleagues examined the effects of sucralose on the hormonal response to a mashed potato meal in overweight individuals and found no significant effect of a sucralose preload on insulin, GLP-1, or GIP [60]. Likewise, NNS co-ingested with a meal of chicken soup and biscuits had no effect on GLP-1 levels in lean males [67]. Similarly, Brown and colleagues found no effect of a sucralose preload on insulin, ghrelin, and glucagon levels in response to a standardized breakfast in lean females [68]. More recently, Tey and colleagues showed that the consumption of drinks containing the NNS, aspartame, stevia, or monk fruit extract when compared with drinks containing sucrose resulted in higher insulin levels at 120 min after lunch, but reported no difference between the four drinks on insulin or glucose area under the curve (AUC) over the 3-h period after lunch [65•].

The longer-term effects of NNS consumption on metabolic regulation in humans have also been examined with no clear consensus on their physiological effects. Two recent studies suggested that sucralose ingestion may negatively affect insulin sensitivity [69, 70]. Lertrit and colleagues showed that 4-week consumption of sucralose (in capsule form) vs. an empty capsule increased peripheral GLP-1 levels and decreased insulin sensitivity in lean, overweight, and obese adults [69]. This finding was replicated by another study showing that a 14-day ingestion of sucralose in beverage form led to decreased insulin sensitivity in lean adults [70]. In contrast, other studies have shown no effect of longer-term NNS consumption on metabolic hormones [18, 71–73]. Ahmad and colleagues found no change in insulin, GLP-1, or leptin levels and no change in insulin sensitivity in lean adults exposed for 12 weeks to aspartame or sucralose mixed in water [71•]. Higgins and Mattes tested 12-week exposure to aspartame, sucralose, saccharin, and stevia in overweight and obese adults and showed no change in insulin levels with any of the NNS examined [18•]. Similarly, another study showed no effects of aspartame and aceK administered in differing dosages over 12 weeks on insulin levels in response to glucose ingestion [72]. Furthermore, Grotz et al. found no difference in glucose, C-peptide, or hemoglobin A1c after ingestion of sucralose in a capsule vs. cellulose placebo over 12–13 weeks in obese and lean adults [74, 75].

Collectively, the current evidence provides equivocal evidence on the effects of NNS consumption on hormones involved in appetite regulation and glucose homeostasis. More work is necessary to determine the specific concentrations and types of NNS that may elicit hormone secretion, whether effects of NNS are dependent on delivery method, and whether consumption of NNS in isolation or in the presence of carbohydrate produces different effects. Future studies should consider how individual characteristics, including habitual NNS consumption, age, sex, adiposity, and insulin resistance, affect metabolic hormone responses to NNS consumption.

Of note, while the majority of work has been done in adults, recent evidence suggests that NNS may affect fetal development and potential programming later in life. Exposure to NNS in utero and during early life was associated with risk of metabolic syndrome later in life in mice [76, 77]. A longitudinal study in children demonstrated that mothers with gestational diabetes who consumed daily NNS compared with NNS non-consumers had children who were larger for gestational age at birth as well as a higher BMI z-score and increased risk of obesity at 7 years [13]. These results were corroborated by a longitudinal cohort study showing that daily consumption of NNS was linked with a 0.2 unit increase in infant BMI z-score as well as a greater risk for being overweight at 1 year of age [11•], suggesting that maternal programming with NNS exposure may affect a child's metabolic development. These studies further underscore the need for studies on the effects of NNS in early development and childhood.

NNS and Neural Systems Involved in Appetite and Reward

There has been increasing interest towards elucidating the effects of NNS on brain regulation of appetite and reward. A growing body of evidence reported via fMRI studies suggests that NNS can provoke differential brain responses in humans, compared with nutritive sweeteners. Frank et al. reported that taste pathways in the brain can distinguish nutritive versus non-nutritive sweet taste; sucrose, relative to sucralose, elicited stronger blood oxygen level–dependent (BOLD) brain response activation of regions involved in reward processing, such as the main gustatory complex (frontal operculum/anterior insula) and the contralateral insula and midbrain, including the ventral tegmental area (VTA), and substantia nigra [78]. In accordance with these findings, Smeets et al. demonstrated that small tastes of sucrose provoked increased BOLD activation in the striatum, while in contrast, small tastes of a mix of several NNS (aspartame, aceK, sodium cyclamate, and sodium saccharin) led to heightened activation in the amygdala, among lean adult males [79]. Taken together, these findings support that either small or large tastes of NNS, when compared with caloric sugars, can evoke differential responses within neural areas involved in processing of reward and primary regions of taste activation.

Notably, several fMRI studies indicate that NNS may have dampened hypothalamic satiety signaling effects, compared with nutritive sugars. The hypothalamus is a brain region that regulates appetite and energy homeostasis. Prior fMRI studies have consistently shown a reduction in hypothalamic activation following the ingestion of glucose, which is interpreted as a biomarker of satiety [80–82], and obesity is associated with an altered glucose-linked hypothalamic response [83, 84]; furthermore, alterations in glucose-linked hypothalamic activation predicted longitudinal weight gain in children [85]. Smeets and colleagues first established that decreases in hypothalamic activation in response to sweetened beverages might be dependent on both sweet taste and energy content. They found that among young adults, glucose ingestion provoked a signal reduction in the hypothalamus, while water, maltodextrin, and aspartame had no effect on hypothalamic activation [86]. Most recently, Van Opstal et al. investigated the hypothalamic response to acute ingestion of sucralose, relative to nutritive sugar; sucralose led to the smallest decrease in BOLD activity in the hypothalamus, similar to water, when compared with glucose, fructose, and sucrose ingestion [87]. Another recent fMRI study also demonstrated that consumption of a fat/protein milkshake sweetened with glucose resulted in a widespread effect on the brain: decreased BOLD signal in the posterior cingulate cortex, brainstem, VTA, and insula and also decreased voxel based connectivity in the hypothalamus and VTA [88••]. In contrast, shakes containing allulose and sucralose showed no effect on BOLD signaling within any of the regions of interest indicating that the NNS had no immediate effect on the activation of brain areas related to eating behavior [88••]. This finding further supports that sweet taste, in the absence of nutritive carbohydrates, may not lead to hypothalamic connectivity changes that are typically linked to satiation. It is important to note that there is an abundant expression of sweet taste receptors within the hypothalamus; RNA expression levels of the sweet taste receptor complex (T1R2/T1R3) in the hypothalamus are significantly higher than those in other brain regions implicated in eating behavior, such as the cortex or hippocampus [89]. Given that NNS interact with the sweet taste receptor complex, future areas of investigation could consider how sweet taste preference impacts neural satiety signaling in response to sugars and NNS.

Other recent findings from Creze and colleagues utilize electroencephalographic (EEG) methods to assess whether ingestion of sucrose and NNS drinks would elicit different neural responses to food cues and subsequent food intake at an ad libitum buffet. The acute ingestion of a NNS beverage (containing a mix of cyclamate, aceK, and aspartame) produced differential neural activity in response to food cues, compared with sucrose and water ingestion. Sucrose or water, but not NNS, led to increased insula activation, whereas NNS consumption increased neural activity in ventrolateral prefrontal regions associated with inhibition of reward, consistent with prior findings in humans [79, 90]. The investigators concluded that their findings showing differential brain responses to acute NNS consumption may be indicative of early-stage adaptation to taste-calorie uncoupling [90••]. However, there was no difference in food intake during the buffet between the water and NNS conditions, which the investigators proposed could be due to limitations in experimental design and that the design may not have been sensitive enough to capture all secondary outcome differences between the NNS and water groups [90••]. Another recent EEG study by Creze et al. featured an interventional design; daily consumers of SSB were asked to undergo a 3-month replacement period with NNS beverage equivalents, which contained a varying mix of NNS, such as aspartame, cyclamate, aceK, and sucralose. Participants neither experienced weight loss over the replacement period nor changes in food liking towards visual cues; however, neural activity in response to high-fat, sweet food cues was decreased in prefrontal regions linked to impulse control after the intervention period [91]. Interestingly, the post-intervention neural modulations in prefrontal areas were predictive of weight loss failure, implying individual diminished ability over food intake control [91].

Additional studies in humans utilizing fMRI methods suggest that frequent dietary consumption of NNS may condition altered neural processing of sweet taste. Rudenga and Small showed a negative association between self-reported chronic NNS use and amygdala response, with a similar trend in the

insula, to acute in-scanner tastes of varying concentrations of sucrose among lean and overweight adults [92]. Given that the amygdala and insula are key regions involved in integrating flavor nutrient signals, these findings are consistent with those of rodent literature suggesting that chronic NNS use may uncouple the association between sweet taste and post-ingestive consequences of predicted calories. In addition, Green and colleagues showed that among individuals who were non-habitual diet soda drinkers, patterns of activation in the orbitofrontal cortex (OFC), a region implicated in processing of reward, differed in response to acute tastes of saccharin compared with sucrose; in contrast, among the habitual consumers of diet sodas, neural activation patterns did not differ between either the sucrose or saccharin condition [93]. Furthermore, habitual diet soda drinkers exhibited greater activation in the OFC, lentiform nucleus, dopaminergic midbrain, and right amygdala in response to both sucrose and saccharin, compared with non-diet soda drinkers [93]. Together, these findings support that chronic NNS consumption may compromise the efficacy of brain regions related to appetite and reward to process sweet taste.

Neuroimaging studies that have assessed brain responses to NNS have largely been focused on lean and healthy cohorts [78, 79, 86, 87, 90–94]. Studies that examine potential obesity related differences in neural responses to NNS are warranted. In addition, many of the neuroimaging studies that examine brain responses to NNS have been limited to same-sex cohorts [78, 79, 86, 87, 90, 91, 94]. Given that sex differences regarding sweet taste perception have been previously reported in rodents [95], future investigators should include both males and females. Finally, to the best of our knowledge, there have been no studies to date that examine the effects of NNS on brain regulation of appetite and reward in children.

Conclusion

While NNS seem to elicit differential brain responses in appetite and reward regions, compared with caloric sweeteners, findings are equivocal as to whether these divergent brain responses are predictive of subsequent metabolic consequences. Gaps in the knowledge include how NNS affect both glucose metabolism and the neural regulation of eating behavior in particularly vulnerable populations such as pregnant and lactating women, children, obese individuals, and persons with metabolic disease. A key goal of future research should investigate how both chronic and acute intake of NNS influence the neural and peripheral responses of these populations. In addition, exposure to NNS during development and throughout the lifespan may also influence sweet taste preferences; given that there is an abundance of sweet taste receptors in the brain, it would be of interest to examine how individual variation in sweet taste preference affects the neural processing of NNS. Considering both the increasing prevalence of dietary NNS intake and the rising rates of obesity and chronic disease, additional studies in humans are critical to determine how NNS consumption impacts neuroendocrine systems across the lifespan.

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Compliance with Ethical Standards

Conflict of Interest The authors have nothing to disclose.

Human and Animal Rights and Informed Consent All cited studies by the authors were approved by the institutional review boards of their respective institutions.

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