Navigating the Sweet Debate: Exploring the Effects of Sweeteners on Physiology

LSC401 Project Research Methods
Unit 2 Literature review
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Abstract

Excessive intake of sugar-added foods is often linked to weight gain, as well as an increased risk of stroke, type 2 diabetes and heart disease. Low-calorie sweeteners (LCSs) with minimal or no calories are commonly used in place of sugar in an attempt to lower the risk of cardiovascular and metabolic conditions. Alarmingly, new research suggests that consuming LCSs raises the risk of cardiovascular death, and that risk is higher in people who are obese or overweight. The most widely used low-calorie sweetener (LCS) in the world, sucrose is an intensive sweetener with no calories that is frequently used by both healthy individuals as well as those with metabolic conditions. This narrative review combines the experimental and clinical findings from recent studies describing the impact of LCSs on systems regulating energy balance and glucose homeostasis in order to investigate a potential causative role for LCSs as a contributor to cardiovascular risk.

Sweeteners: Boon or Bane? Exploring Their Impact on Society

Providing sweet-tasting, low-energy items to customers seems to be the magic bullet for improving weight reduction and lowering the rates of cardiometabolic illness (Reid et al., 2016). Low-calorie sweeteners (LCS), also referred to as sugar substitutes, are food additives designed to replicate the taste of sugar used to reduce calorie intake but keep the sweet taste (Chattopadhyay et al., 2011). However, the question arises: has the use of LCS contributed to the obesity, metabolic syndrome, and diabetes epidemics that have overtaken society since 1980? Has the widespread use of these products—especially among the most vulnerable—fuelled our epidemics of obesity and its aftereffects? Or if LCS hadn't been so extensively utilised, might it have been much worse?

Metabolic diseases have a major impact on society, thus understanding the rationale behind where the process initiates and why it is crucial to cease at a certain juncture is essential. Metabolic diseases like obesity, non-alcoholic fatty liver disease or diabetes mellitus are not only a US-specific issue. By 2045, an estimated 783 million individuals may have diabetes, with 537 million affected by type 2. Additionally, around 352 million have impaired glucose tolerance, with 5–10% at risk of developing type 2 diabetes annually (Ahmad et al., 2022). In a similar vein, non-alcoholic fatty liver disease, affecting 25% globally, correlates with metabolic diseases like obesity, hypertension, and dyslipidemia (Fan et al., 2018). In a 2016 modelling study, yearly expenses for non-alcoholic fatty liver disease (NAFLD) were assessed and findings revealed $103 billion in the US, equating to $1613 per patient, and €35 billion across Europe, ranging from €354 to €1163 per patient. This substantial economic burden primarily stems from NAFLD's impact on obesity, cirrhosis, and type 2 diabetes (Eguchi et al., 2020).

LCSs consumption in the United States surged rapidly between 1980 and 1988 once a methyl ester of aspartic acid and phenylalanine called aspartame was introduced as a countertop sweetener in 1981 and as a component in diet beverages, other drinks and foods in 1983. A sharp rise in the prevalence of obesity in the US occurred between the end of the National Health and Nutrition Examination Survey (NHANES) II which was conducted from 1976 to 1980 and NHANES III, which was conducted from 1988 to 1994 (Yang, 2010). Interestingly,

before 1980, the primary LCS in the United States for a century was saccharin, a coal-tar derivative that was mostly sold to people with diabetes and eaten at relatively low amounts (Flegal et al., 1997). The introduction of sucralose (1998), acesulfame potassium (AceK: 2002), neotame (2003), and advantame (2014) as well as the introduction of monk fruit and stevia extracts in 1994 and 2010, respectively, all may have contributed to the rise in obesity prevalence over the following three decades (Science History Institute, 2023).

This study presents a narrative review of the data and research available about the use of low-calorie sweeteners and their possible impact on the trends of glucose metabolism, hormone regulation and consequently, metabolic diseases. Along with integrating the available data, the goals of this literature review are to point out knowledge gaps and advance the understanding of the complex relationship between sweeteners and the epidemiology of metabolic diseases.

Potential Mechanisms of Action of Low-calorie sweeteners on Sweet Taste Perception: From Sensory Perception to Metabolic Impact.

1.1. Overview of Low-Calorie Sweeteners: Types, Usage, and Metabolic Effects

Low-calorie sweeteners (LCSs) are known for their ability to create a sensation of sweetness by stimulating the mechanisms responsible for perceiving sweetness. They have been employed in food and drink products more frequently since high-energy added sugars have been linked to negative health effects such as cardiovascular diseases, obesity and type 2 diabetes (Science History Institute, 2023). Low-calorie sweeteners are classified into various categories based on their source (such as natural or artificial), their sweetness intensity, and their nutritional properties (including caloric or noncaloric content) (Lee & Owyang, 2017). Natural sweeteners refer to the monk fruit (Siraitia grosvenorii), stevia, swingle fruit extract, and thaumatin, the sweet-tasting protein. Among artificial sweeteners commonly used include saccharin, advantame, acesulfame potassium (acesulfame-K), neotame, sucralose and aspartame (Risdon et al., 2021).

Developed at Johns Hopkins University in 1879, saccharin is the oldest artificial sweetener. With a sweetness level 200 to 700 times higher than sucrose, it is used in a wide range of products, including soft drinks, salad dressings, candy, chewing gum, and non-edible items such as toothpaste, medications, and mouthwash (SM, 1986). Conversely, sucralose is the most widely used artificial sweetener in the world, making up 30% of the US$2.29 billion global market for LCS in 2016. Approximately 600 times sweeter than sucrose, sucralose closely mimics the taste and temporal profile of sucrose (Laffitte et al., 2016). This sweetener has been approved by both the European Food Safety Authority and the FDA, establishing an acceptable daily intake of 15 and 5 mg/kg/d, respectively. Sucralose is approved for use in various food items such as beverages, baked goods, chewing gum, frozen dairy desserts, and gelatins (European Commission, 2023).

In 2001, researchers led by Nelson discovered that several studies later confirmed: sweet-tasting compounds such as natural null-caloric sweeteners, natural sugars, and artificial sweeteners are identified by a sweet-taste receptor found on the outer surfaces of taste receptor cells found within the taste buds situated in the oral capacity (Nelson et al., 2001). After detection, the signalling cascade in taste bud cells starts with the stimulation of α-gustducin, the heterotrimeric G-protein, followed by the activation of phospholipase C (PLC) β2 (Calvo & Egan, 2015). This causes the transient receptor potential cation channel M5 to become activated in a calcium-dependent manner, exposing Pannexin-1, depolarizing the membrane, and eventually releasing ATP. Consequently, principal afferent sensory fibres are stimulated by extracellular ATP, leading them to transmit a signal of sweet taste to the brain (Mace et al., 2007). Beyond their role in initiating sweet sensation in the oral cavity, there is increasing evidence suggesting that taste receptors serve as nutrient sensors and play a key role in metabolic regulation. Research indicating their involvement in, metabolism, glucose intestinal absorption, and cardiovascular functions has laid the foundation for the development of novel therapeutic approaches (Risdon et al., 2021).

1.2. Sweet Taste Perception and Signal Transduction Pathways in Taste Bud Cells

The sense of sweetness is detected through sweet taste receptors present on the taste buds of the palate and tongue (Kim et al., 2019). These receptors are composed of a heterodimer, formed by the subunits of T1R3 and T1R2, belonging to class C, G-protein coupled receptors (GPCRs). Studies using knockout mice and cellular assays have confirmed that the TAS1R2/TAS1R3 heterodimer serves as the principal sweet-taste receptor (Damak et al., 2003). The structure of these proteins includes a 7-transmembrane-helix attached to a Venus flytrap domain by a short cysteine-rich linker. Both natural monosaccharides, disaccharides, and artificial sweeteners like sucralose interact with the domain of the Venus flytrap of the subunits TAS1R2 and/or TAS1R3 (Kojima et al., 2014). While sucrose can trigger TAS1R2/TAS1R3 at extremely high doses (>300 mM), the majority of LCSs are far more potent agonists, activating these taste receptors at considerably smaller amounts (<100 μM) (Zhang et al., 2010).

Following the detection of sweet substances by G-protein coupled receptors, specifically the T1R3 and T1R2 receptors located in the lingual epithelium, cascade signalling is initiated with the dissociation of gustducin, known as the taste G-protein (Thompson et al., 2014). Upon activation, the subunits of gustducin, including Gβγ and Gα, carry out their functions by activating phospholipase C β2 (Gβγ) and inhibiting cyclic AMP production (Gα). This activation leads to the hydrolysis of PIP2, triggering the production of diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). IP3 stimulates the endoplasmic reticulum to release Ca2+, which opens the melastatin type-5 transient receptor potential cation channel (TRPM5) to allow for the entry of Na+ ions (Liu & Liman, 2003).

Cell depolarization is made possible by increases in intracellular Na+ and Ca2+. This stimulates intermediate neurons, glossopharyngeal nerves, and the chorda tympani, which then send taste data centrally to the insular cortex via ATP-dependent and 5-hydroxytryptamine pathways. As a result, primary afferent sensory fibres are activated by extracellular ATP, causing them to transmit a signal indicating the perception of sweetness to the brain (Zhang et al., 2003).

1.3. Taste Perception and Reward-Related Pathways in Appetitive Behaviors

It is well acknowledged that the sensation of taste influences neural processes that generate aversion and reward, hence guiding fundamental appetitive behaviours (Risdon et al., 2021). Research employing lab-based rodent models shows that it is feasible to directly affect an animal's internal representation, sensory perception, and behavioural behaviours (i.e., sucrose appetency) by modifying the brain regions associated with sweet taste (Peng et al., 2015).

Chronic activation of analogous reward-related pathways in humans, facilitated by highly appealing foods including sugar, is considered to be able to overcome homeostatic signals, ultimately resulting in obesity and overeating (Beilharz et al., 2014). Behavioural investigations support this notion by demonstrating that, even when full, rodent models enhance their daily fluid consumption by nearly entirely drinking the sugar solution when given the option between it and water (Yin et al., 2019). It's interesting to see that behaviour and affinity to sweeter materials are the same when LCS are used in place of sugar (Bachmanov, 2001).

However, each LCS reports disparities in perceived taste, which results in various hedonic reactions. The majority of LCSs bind to TAS2R and produce a bitter aftertaste that is more pronounced at higher doses (Wiet & Beyts, 1992). According to a number of clinical studies, sucralose has a more tolerable sucrose-like flavour than saccharin or acesulfame-K due to the fact that it is less bitter (Schiffman et al., 1995; Birch & Mylvaganam, 1976; Sclafani & Ackroff, 2017). TAS1R2/TAS1R3, which detects both sugar and sweeteners, is known to be a peripheral mediator of sweet taste perception (Damak et al., 2003). Remarkably, sweet receptor-inhibited ageusic rats eventually acquire a preference for sugar but not for LSCs, suggesting that sugar can activate other reward pathways (Sclafani et al., 2014).

This is supported by clinical brain imaging statistics, which show that sucralose and sucrose both engage taste-reward pathways. However, reactions to sucrose seem to be stronger and include more pleasure-related brain regions (Frank et al., 2008). The evidence that is now available indicates that the combination of both postingestion and orosensory signals contributes to an attraction to and predilection for sweeter components (Risdon et al., 2021).

Zuker's group has recently discovered a gut-to-brain neural circuit that transmits sugar information to the brain and determines the desire for sugar (Tan et al., 2020). The sodium-glucose cotransporter (SGLT), which only responds with specific hexoses (such as glucose and galactose) and fails to recognise any of the LCSs, provides the basis for this postoral identification mechanism (Sclafani et al., 2015). This particular finding may help to explain why, after extended exposure, glucose and sucrose are more satisfying than sucralose (or comparable sweeteners). According to the prevalent paradigm in eating control, the previously mentioned hedonistic system and the homeostatic mechanism are two parallel systems that interact to affect food consumption (Sclafani et al., 2010).

A number of hormone regulators, including peptide tyrosine-tyrosine (PYY), insulin, ghrelin, leptin, and glucagon-like peptide type 1 (GLP-1) that signal the cerebral cortex about peripheral energy reserves, are essential to the homeostatic system (Jang et al., 2007). Carbohydrates encourage the release of these chemicals in the stomach, which signals fullness (Temizkan et al., 2015). Sucralose is a strong inducer of glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 production in the enterocyte, according to several in vitro investigations that have shown this to be regulated by the sweet receptor TAS1R2/TAS1R3 52. While sucralose ingestion did not alter leptin levels in clinical or animal investigations, it appears that this molecule has an impact on ghrelin (Wu et al., 2012). However, the outcomes of clinical and in vivo investigations fluctuate (Ford et al., 2011). Hence, further comprehension and research are necessary to fully understand the relevance of these systems for controlling hunger and food intake.

1.4. Beyond the Mouth: Expression and Signaling of Taste Receptors in Non-Gustatory Pathways

It's noteworthy to observe that taste receptors, initially identified in the mouth, have been shown to be expressed in several non-gustatory pathways (Young et al., 2008). Both TAS1R2 and TAS1R3 are actively expressed in several tissues, including the brain, stomach, pancreas, and adipose tissues (Nelson et al., 2001). However, TAS1R3 is exclusively produced, possibly in a homodimeric structure, via its monomeric component in several other tissues, such as the stomach, liver, lymphocytes, kidney, lung, and presumably the endothelium. According to cellular experiments, TAS1R3 is not particularly responsive to mono- and disaccharides when it is by itself, i.e., when TAS1R2 is absent (Xin & Chen, 2017). It has been hypothesized that the TAS1R3 homodimer may have a role in the identification of sucralose, notwithstanding the absence of compelling data (Nakagawa et al., 2013). Additionally, several TAS2Rs, encompassing various sucralose-sensitive variants, have also been discovered in other tissues like the vascular wall and heart (Xin & Chen, 2017).

The canonical pathway, initially discovered in taste buds, is largely linked to the activation of the sweet taste receptors (TAS1R2/TAS1R3) and bitter taste receptors (TAS2R), when stimulated by sucralose or any other LCS in these other tissues (Kojima et al., 2014). Nevertheless, current research also indicates that taste receptors may activate other signalling pathways. In this case, Nakagawa and associates presented findings that LCSs function as predisposed agonists targeting TAS1R3 in mice insulinoma 6 cells,

activating different signalling systems (Nakagawa et al., 2013). For instance, these cells exhibit unique activation of the adenylate cyclase and/or PLC pathways in reaction to interactions with acesulfame-K, sucrase or Na-saccharin with TAS1R3. This results in a differential response pattern to variations in cAMP and/or intracellular calcium concentrations (Nakagawa et al., 2009).

Pancreatic β cells also include receptors for sweet taste (Nakagawa et al., 2009). Studies conducted in vitro have demonstrated that LCSs like saccharin, acesulfame-K, and sucralose stimulate the TAS1R3/TAS1R2, which in turn stimulates the release of insulin (Kyriazis et al., 2014; Roberts et al., 2000). Even though ATP is not produced during the contact between LCS and pancreatic β cells to depolarize the cell membrane and stimulate insulin release, this effect is induced by activating the sweet taste receptors through cAMP-dependent and cytoplasmic calcium pathways (Nakagawa et al., 2009). Sucralose has been shown to enhance the production of insulin when glucose is present in experiments with isolated pancreatic islets from rats (Malaisse et al., 1998; Hara et al., 2007). Nonetheless, several studies have shown that humans absorb sucralose minimally or not at all (Roberts et al., 2000, Rother et al., 2018). Thus, there is a small likelihood that sucralose has any interaction with the β cells in the pancreas, and its effects on metabolism are probably produced only in the gastrointestinal tract (Risdon et al., 2021).

Nevertheless, it is unclear if LCSs' activity on taste receptors results in physiological changes in regular consumers because the majority of their effects have only been seen in vitro. In fact, there are arguments against the theory that sucralose causes taste receptors in some organs to become active. Sucralose's pharmacokinetics have not been well studied, however, prior studies have shown that its oral bioavailability is relatively low—approximately 14% (Roberts et al., 2000). This appears to be unique to the sucralose molecule as other LCSs that are frequently used in the beverage and food industry, like saccharin or acesulfame-K, absorb 80–100% into the plasmatic compartment and are therefore more probable to reach a plasmatic concentration sufficient for TAS1R activation (Magnuson et al., 2016). Sucralose plasma concentration, however, is mostly reliant on gastrointestinal permeability, which may be heightened in diseases like diabetes and obesity (Duncan et al., 2008; Ding et al., 2010). Lastly, in order to fully comprehend the impact of consuming sucralose on human health, there is a lack of scientific information about the role of sucrase in nondigestive tissues.

1.5. Impact of Low-Calorie Sweeteners on Glucose Regulation: Conflicting Evidence and Long-Term Effects

Numerous mechanisms have been proposed to explain how LCs may affect insulin and glucose concentrations. These include changes in the gut microbiota, increased activation of glucose transporters, and stimulation of incretin release through interaction with sweet taste receptors found in the pancreas and intestine (Romo-Romo et al., 2017). Nevertheless, research describing how LC intake affects glucose regulation has shown conflicting results (Pepino, 2015). Variations in the outcomes are caused by variations in the sweetener matrix

as well as whether the sweetener is consumed on its own or in conjunction with a calorie or glucose load to induce changes in glucose and insulin concentrations (Tucker & Tan, 2017).

Romo-Romo et al. found that sucralose consumption was unrelated to changes in insulin, human fasting glucose, or glycated haemoglobin (HbA1c) in their systematic review of studies published between 1996 and 2012. It should be stated, nevertheless, that the majority of the research publications they looked at had only examined the immediate effects of only one exposure to sucralose. These acute exposure trials included levels of sucralose ranging between 60 mg and 1000 mg, which were given as capsules, commercial granular sucralose, pure sucralose, or diet soda containing sucralose. These treatments were administered using intraduodenal and intragastric infusions, either on their own, prior to a typical meal or an oral glucose tolerance test (OGTT). Regarding the implications of regular sucralose consumption, two human investigations conducted by the same study group found no differences in HbA1c, insulin, fasting glucose, or C-peptide after 12 and 13 weeks of sucralose consumption, respectively. However, it should be mentioned that in those studies sucralose was given on a daily basis using capsules of 333 and 667 mg, respectively (Romo-Romo et al., 2016).

According to Pepino et al.'s research, four investigations have demonstrated a substantial decrease in insulin sensitivity following exposure to sucrose. In one study, only one exposure to 48 mg sucralose resulted in increased insulin, glucose, and C-peptide concentrations at specified time-points and a 23 ± 20% ($P = 0.01$) loss in insulin sensitivity after a 5-hour oral glucose tolerance test (OGTT) for 17 adults with chronic obesity when compared with water drinking (Pepino et al., 2013). Additionally, Nichol et al. demonstrated that both obese and normal-weight subjects experienced a 30 ± 10% greater glucose AUC ($P = 0.03$) following an OGTT when acutely exposed to 48 mg of sucralose as opposed to water. Furthermore, the production of insulin was elevated in participants with obesity at 90–120 minutes following the start of the OGTT, although it reduced in normal-weight participants 20–40 minutes later ($P < 0.05$). It is remarkable that this study found that only sucralose ingestion increased glucose AUC during OGTT, not sucralose flavour or expectoration in people who were both normal weight and obese. However, oral sensation alone could potentially yield metabolic effects, as demonstrated by the significant dampening of plasma insulin rise observed when tasting sucralose before consuming a glucose drink (Nichol et al., 2019).

In terms of long-term effects, healthy subjects who ingested daily capsules comprinsing 200 mg of sucralose for a period of 4 weeks experienced a significant ($P< 0.01$) decrease in insulin sensitivity, as indicated by reductions in the homeostasis model assessment of insulin sensitivity (HOMA-%*S*) and the Matsuda index. Conversely, there was a rise in both the insulinogenic index during an oral glucose tolerance test (OGTT) and the homeostasis model assessment of β-cell function (HOMA-%B) (Lertrit et al., 2018). After an intravenous glucose tolerance test, when healthy, lean subjects were instructed to take sucralose (15% of the recommended ADI) for a duration of 14 days, a reduction in insulin sensitivity was also seen (Romo-Romo et al., 2018). On the contrary, Dalenberg et al. showed that consuming drinks with 31.83 g of maltodextrins and 60 mg of sucralose for two weeks significantly raised the AUC of insulin ($P < 0.01$). However, this was not the same for drinks with sucralose or maltodextrins alone. The participants in this study were adults and teenagers. However, a

significant shift in the HOMA-IR in the sucralose/maltodextrin group led to the suspension of the experiment for the teenagers (Dalenberg et al., 2020).

Margolskee et al. demonstrated using animal models that SGLT1 expression increased in enteroendocrine cells on a diet low in carbohydrates enriched with sucralose and other LCSs (such as saccharin and acesulfame-K, excluding aspartame). Since this effect was not reproduced in α-gustducin and TAS1R3 mutant animals, the enhanced expression seems to be the result of the binding of LCS with the sweet taste receptors, α-gustducin and TAS1R3 (Margolskee et al., 2007). In the small intestines of rats, Mace et al. discovered that LCS enhanced the apical activity of glucose transporter 2, which is controlled by the sweet taste receptors, TAS1R3, TAS1R2 and α-gustducin. Acesulfame-K showed the most significant increase in glucose absorption induced by LCS, then followed by sucralose and, to a smaller degree, saccharin. These findings imply that LCSs can enhance the enterocyte's ability to transport glucose both actively and passively (Mace et al., 2007). In comparison to rats that consumed sucrose, sucralose consumption during a 4-month period enhanced insulinemic and glycemic responses, according to a recent study conducted in male Wistar rats. These outcomes were coupled with diminished phosphorylation of protein kinase B and insulin receptor substrate 1, as well as reduced levels of SREBP-1 and glucose transporter 4 expression in the baseline condition (Sánchez-Tapia et al., 2019).

For a long time, including the present, sucralose has been thought to have no effect on the metabolism of glucose (Ahmad et al., 2020). The approaches employed in these studies, such as fasting insulin and glucose, HbA1c, and OGTT, are not sufficiently sensitive to ensure that LCSs do not affect glucose homeostasis (Romo-Romo et al., 2016). Furthermore, a large number of these investigations have been crossover trials using only one sucralose dose (Ahmad et al., 2020). Parallel-randomized clinical trials with more accurate methods, like the hyperinsulinemic euglycemic glucose clamp, are required to detect early alterations in factors like insulin sensitivity that may make an individual more susceptible to serious disruptions in glucose tolerance after prolonged exposure to sucrose.

1.6. Incretin Hormones: Role in Glucose Regulation and Impact of Sucralose Consumption

Intestinal peptides known as incretins function as hormones responsible for approximately 50% of postprandial insulin production, which is reliant on glucose (Nichol et al., 2019). GIP and GLP-1 are the primary incretins. There is proof that incretins have a part in pancreatic neogenesis and β-cell apoptosis prevention (Grotz et al., 2017). When GLP-1 is administered to individuals, it increases sensations of fullness, which decreases food intake and ultimately aids in weight reduction (Gutzwiller et al., 1999). The central nervous system's management of food intake and slow digestion are the principles behind this effect (Shah & Vella, 2014).

GIP falls into the category of gut hormones that stimulate the release of insulin from pancreatic islet β cells when food is consumed, but specifically in the presence of elevated

blood glucose levels. Increased GIP secretion is primarily triggered by glucose within sucrose (Holst, 2004). A recent study conducted by Pfeiffer and colleagues suggests that sucrose, owing to its distinctive structure, independent of its calorie content, induces heightened secretion of the gastrointestinal glucose-dependent insulinotropic peptide (GIP) (Prinz, 2019). Sucrose triggers a rapid release of GIP (glucose-dependent insulinotropic polypeptide) in the body, with peak levels observed around 15 minutes after consumption. This release aligns with the initial secretion of insulin in healthy individuals (Maeda et al., 2013). Research comparing the impact of GIP and GLP-1 (glucagon-like peptide-1) on insulin secretion following oral sucrose intake has demonstrated that GIP plays a predominant role, while GLP-1 contributes to a lesser extent in healthy subjects (Vilsbøll & Holst, 2004). Consequently, this mechanism may contribute to heightened appetite, body weight, and the potential development of insulin resistance (Holst, 2004).

Sucralose has been shown to selectively enhance GIP and GLP-1 production in a number of animals and in vitro experiments. The reactions that occur among TAS1R3, α-gustducin, and TAS1R2, which are found in K cells and enteroendocrine L cause this rise in incretins. However, as previously noted, it might also be caused by a rise in SGLT1 production induced by sucralose (Daly et al., 2012). A number of studies conducted on the rat's small intestine tissue revealed that sucralose's impact on incretins is dependent on dose; nevertheless, other investigations revealed that increased sucralose concentrations do not enhance incretin production (Pepino, 2015; Jang et al., 2007).

Contradictory findings have been found in several human investigations assessing the impact of sucralose on incretin secretion. Sucralose was ingested alone in all trials that showed no impact on GIP and GLP-1 secretion. These studies included dosages that varied between 40 to 960 mg. They were all crossover trials that assessed the effects of sucralose after the sweetener was administered once (Ma et al., 2010; Steinert et al., 2011; Ford et al., 2011). When contrasted with sucralose by itself, studies that conducted an OGTT following sucralose ingestion revealed greater GLP-1 concentrations, indicating that a mixture of this LCS with glucose amplifies incretin production. These studies employed dosages that varied between 24 to 200 mg, and each investigation had a crossover design (Temizkan et al., 2015; Brown et al., 2012; Lertrit et al., 2018). It is noteworthy, therefore, that two investigations that used an OGTT following sucralose ingestion reported no shift in GIP and GLP-1 concentrations (Ahmad et al., 2020; Pepino et al., 2013).

Higher amounts of GLP-1 were found when sucralose was taken routinely at a dose of 200 mg/d for four weeks. Nonetheless, a recent study found that giving healthy individuals frequent sucralose over a two-week period did not affect the fasting plasma levels of hormones that control appetite, such as ghrelin, GLP-1, and PYY (Romo-Romo et al., 2020). In two of the trials where sucralose was shown to affect GLP-1 production, the subjects were either type 1 or type 2 diabetics. Only those experiencing type 1 diabetes and healthy individuals had higher amounts of GLP-1; individuals with type 2 diabetes were not affected (Brown et al., 2012; Temizkan et al., 2015). Since GLP-1 secretion affects appetite and the production of insulin, people with type 2 diabetes may benefit from a boost in GLP-1

production for overall health. There are no reports of sucralose's impact on GIP in people (Risdon et al., 2021).

Concluding Remarks: Implications of Low-Calorie Sweeteners on Cardiovascular and Metabolic Health

Since it is difficult to investigate the impact and pathways of individual LCSs independently, the majority of scientific literature, particularly epidemiological studies, treats low-calorie sweeteners as a broad family of compounds. It is essential to bear in mind, however, that each type of LCS varies significantly in terms of its pharmacological efficacy, pharmacokinetic profile, and chemical structure. Since sucralose represents one of the LCSs that is most often used in food and beverages worldwide, most of the studies concentrated on the particular impact that regular sucralose intake has on cardiovascular and metabolic health. Sucralose and other LCSs bind to the same class of cellular receptors (TAS1R3/TAS1R2, TAS2Rs, and TAS1R3/TAS1R3), however, their affinities differ, and an LCS by itself can also act as a biassed agonist. Sucralose is a particular pharmacological substance that causes both pathological and physiological reactions in humans, nevertheless, nothing has yet been discovered regarding its distribution in nondigestive cells. To have a better understanding of the impact of consuming LCSs on human health, this crucial question still has to be answered.

Therefore, additional research is required to determine the minimum amount of LCSs that may be ingested before it may enter the circulation and affect the cardiovascular system directly. It should be noted that in order to understand the underlying processes behind the inconsistent findings on the effects of LCSs consumption on metabolism and the cardiovascular system that have been shown in studies involving both humans and animals, preclinical research and prospective randomised clinical trials are crucial. Taking everything taken into account, the information found in this analysis raises grave concerns and strengthens the case for more studies to determine whether regular LCSs consumption has any negative health effects and if so, whether it increases the chance of developing cardiometabolic diseases throughout life.

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