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Review

Do non-nutritive sweeteners influence acute glucose homeostasis in humans? A systematic review

Robin M. Tucker[a], Sze-Yen Tan[b,c,*]

[a] Department of Food Science and Human Nutrition, Michigan State University, East Lansing, MI, USA
[b] School of Pharmacy and Medical Sciences, Alliance for Research in Exercise, Nutrition and Activity (ARENA), University of South Australia, City East Campus, North Terrace GPO Box 2471, Adelaide, SA 5001, Australia
[c] Clinical Nutrition Research Centre (CNRC), Singapore Institute for Clinical Sciences (SICS), Agency for Science, Technology and Research (A*STAR), National University Health System, Singapore

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ABSTRACT

The human body associates sensory cues with metabolic consequences. Exposure to sweet-tasting sugars – even in the absence of ingestion – triggers physiological responses that are associated with carbohydrate digestion, absorption and metabolism. These responses include the release of insulin and incretin hormones, which work to reduce blood glucose. For this reason, non-nutritive sweeteners (NNS) have been posited to trigger similar physiological responses and reduce postprandial blood glucose concentrations. The first part of this review presents a brief overview of sweet taste receptor activation in the oral cavity and gastrointestinal tract and the ensuing physiological responses related to glucose homeostasis. The second part of this review contains a systematic literature review that tested the hypothesis that NNS use improves glucose regulation postprandially. Studies were grouped based on sweet taste receptor stimulation paradigms, including pre-ingestive stimulation, ingestion of NNS alone, co-ingestion of NNS with foods, and using NNS as preloads to influence subsequent blood glucose excursions. In summary, the review found that NNS triggered physiological responses, albeit inconsistently, yet failed to significantly lower blood glucose levels in almost all studies.

1. Background

1.1. Principles in regulating postprandial glycemia

The prevalence of type 2 diabetes continues to increase and finding effective strategies to regulate blood glucose levels is critical. While fasting blood glucose levels have been used as an indicator of glucose management, controlling postprandial blood glucose, i.e. lowering glucose peaks and fluctuations, is key to preventing long-term health consequences [1,2]. Maintenance of blood glucose within a specific range is referred to as glucose homeostasis, which involves the regulation of glucose appearance into and glucose clearance from the bloodstream. In addition to limiting carbohydrate load, several other approaches have been proven to be effective in promoting glucose homeostasis, including modifying carbohydrate structure by altering the amylose-to-amylopectin ratio [3] or increasing the proportion of dietary fat [4] and fiber content [5] of a meal to modulate postprandial glycemic responses. These approaches either reduce the digestibility of carbohydrate, slow the gastric emptying rate, slow the absorption rate of glucose, or stimulate hormones (such as incretins and insulin) that facilitate the transportation of glucose out of the blood and into metabolically active tissues in the body [6]. One emerging area of study in the quest to optimize postprandial glucose homeostasis involves sweet taste stimulation. The premise of this strategy is that sweet taste stimulation by nutritive sweeteners in the oral cavity has been shown to trigger physiological responses that prime the body for impending carbohydrate ingestion and regulate glucose homeostasis [7]. In addition, others have posited that NNS, which stimulate sweet taste receptors, might also promote glucose homeostasis [8]. This paper first provides a brief overview of how and where sweet taste is detected and the effective stimuli that activate sweet taste receptors followed by a systematic review that presents the evidence of whether sweet taste from NNS influences glucose homeostasis.

1.2. Sweet taste receptors: oral cavity and beyond

Historically, sweet taste receptors, T1R2 and T1R3, were first identified in the oral cavity, [9] where they were observed to detect sweet-tasting stimuli such as sweet carbohydrates. However, recent studies have located sweet taste receptors elsewhere including the

* Corresponding author at: School of Pharmacy and Medical Sciences, University of South Australia, City East Campus, North Terrace GPO Box 2471, Adelaide, SA 5001, Australia.
E-mail address: SzeYen.Tan@unisa.edu.au (S.-Y. Tan).

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gastrointestinal (GI) tract, lungs and pancreas [10–12]. An important difference between oral sweet taste and GI sweet taste is that the activation of GI sweet taste receptors does not allow the sensation of sweetness to be perceived. Even though sweetness is not perceived by the brain through the activation of GI sweet taste receptors, evidence shows that the activation of sweet taste receptors at this site triggers physiological changes; [13] thus, the physiological responses discussed in this review are therefore attributed to the activation of sweet taste receptors rather than sweet taste perception.

1.3. Sweet stimuli: Nutritive and non-nutritive

Each subunit (T1R2 and T1R3) of the G-protein coupled sweet taste receptor is capable of binding to sweet stimuli [14]. This characteristic explains the wide variety of stimuli capable of activating sweet taste receptors in the oral cavity and GI tract [14,15]. Stimuli capable of activating sweet taste receptors can be broadly separated into two categories: nutritive and non-nutritive sweeteners (NNS). Nutritive sweeteners, like glucose, fructose, and sucrose, are digested and metabolized by the human body after being ingested. Most NNS possess high-potency sweetness (some exceptions include sugar alcohols), [16] so only a very small amount of these compounds are used in foods and beverages and, thus, contribute negligible nutrition and energy. Eight NNS are currently regulated as food additives by the U.S. Food and Drug Administration (FDA): advantame, aspartame, acesulfame-K, neotame, saccharin, and sucralose, while stevia (active compounds: stevioside and rebaudioside) and monk fruit extracts (active compounds: mogrosides) are also considered naturally-occurring NNS that are currently available to consumers [17].

1.4. Evidence that sweet taste receptor activation influences glucose homeostasis

The importance of sweet taste receptor activation on glucose homeostasis has been demonstrated via the activation of sweet taste receptors at two major sites: the oral cavity and the gastrointestinal (GI) tract. The activation of oral sweet taste receptors while bypassing GI sweet taste receptors is achieved via sham-feeding in animals or modified-sham feeding (chew/swish-and-expectorate) in humans. The biggest advantage of oral-only sweet taste receptor stimulation is that this method minimizes the effects of nutrients since stimuli are not ingested; hence, post-stimulation physiological responses are attributed largely to oral-only sweet taste. Pre-ingestive oral stimulation results in a number of physiological changes that are referred to as cephalic phase responses [18]. Based on animal and human research, cephalic phase responses generated by oral-only sweet taste stimulation include increases in all of the following: salivary flow, lingual α-amylase concentrations, [19,20] insulin and glucagon release by the pancreas [21] and glucose absorption [22]. These responses suggest a role for oral-only sweet taste receptor activation in promoting glucose homeostasis.

The other major site involved in glucose homeostasis through the stimulation of sweet taste receptors is the GI tract. This stimulation occurs in one of two ways – either via ingestion of sweet stimuli or by circumventing oral sweet taste stimulation and sweet taste perception by the use of capsules or intragastric infusion. Thus, capsules or intragastric infusions give the most accurate assessment of the importance of GI sweet taste receptor activation on glucose homeostasis.

The effects of sweet taste receptor activation on glucose homeostasis were demonstrated in several elegantly designed experiments. In these experiments, scientists compared the physiological responses induced by sugar solutions under two conditions – with and without fully functional sweet taste receptors and/or transduction mechanisms. In animal models, wild type mice vs. mice with impaired sweet taste receptor function, e.g., knock outs (KO) of T1R3 or taste-cell signaling components like α-gustducin, which inhibited sweet taste receptor activation and/or transduction, were compared. In wild type animals, sweet taste receptor activation from sugars over two weeks stimulated the expression of SGLT-1 (glucose transporter), [23] and acute GLP-1 [13] release. In comparison, KO animals had lower glucagon-like peptide 1 (GLP-1), glucose-dependent insulinotropic peptide (GIP) and insulin responses compared to their wild type counterparts, which resulted in significantly higher plasma glucose in the KO mice [13,24]. These studies highlight the role of sweet taste receptor activation in glucose homeostasis. In humans, where the knockout of sweet-taste-related genes is not possible, sweet taste receptors were blocked with negative allosteric modulators such as lactisole, gymnemic acid, zizyphins, and hodulcin [25]. Similar to animal models, the intragastric infusion of glucose solution was observed to elevate plasma GLP-1, but the effect was attenuated significantly, albeit not totally, when GI tract sweet taste receptors were blocked by lactisole [26]. The incomplete attenuation of GLP-1 release by lactisole in humans might be explained by: 1) failure of lactisole to block sweet taste receptors throughout the entire gastrointestinal tract, 2) incomplete blockage of sweet taste receptors by lactisole, which has been shown to be an antagonist that targets human T1R3 only, [27] or 3) that there may be alternative means of stimulating GLP-1 release by non-taste factors via the taste-signaling transient receptor potential type M5 (TRPM5) ion channels [28]. While the evidence is most compelling in animals, it suggests that oral and GI sweet taste receptors play important roles in glucose homeostasis.

While nutritive sweeteners appear to play an important role in glucose homeostasis, NNS also activate sweet taste receptors. Because of this relationship, some researchers have posited that NNS might serve to decrease blood glucose as the physiological responses that lower blood glucose would be activated [29] but without the accompanying carbohydrate load to increase glucose concentrations. This paper presents a systematic review that examines the effects of NNS on acute postprandial glucose homeostasis.

2. Effects of non-nutritive sweeteners on human glucose homeostasis

The effects of NNS on a wide range of factors related to blood glucose regulation, such as insulin, glucagon, incretins (GLP-1 and GIP), gastric emptying rate, and glucose absorption rates were considered to provide a more complete picture of how NNS influence glucose homeostasis.

2.1. Systematic review strategies

A systematic literature search of the electronic databases PubMed, Web of Science, and CINAHL was conducted. When possible, studies were filtered by English language, adults, and humans. As an example, the following search string in PubMed was used: (((“Sweetening Agents”[Mesh]) AND “Blood Glucose”[Mesh]) AND Humans[Mesh] AND English[lang]). Additionally, we searched through review articles and identified additional qualifying studies that were missed by the electronic searches. Studies were included in the review if they met the following criteria: 1) included human adult subjects published prior to November 1, 2016 - an updated search was conducted on June 5, 2017, to identify additional articles that had been published since the original search was conducted; 2) used at least one NNS – defined as: advantame, aspartame, acesulfame-K, neotame, saccharin, and sucralose, stevia, and monk fruit extracts (Luo Han Guo) as these are approved by the FDA or are considered Generally Recognized as Safe (GRAS) [30]; 3) tested healthy or diabetic participants; 4) measured glucose homeostasis outcomes (glucose, insulin) or other factors associated with glucose homeostasis (glucagon, incretins (GLP-1 and GIP), gastric emptying rate, and glucose absorption rates); 5) were crossover acute postprandial trials (measurements taken ≤ 24 h after exposure to NNS); 6) tested cephalic phase or postprandial effects of NNS; 7) tested NNS alone, with a meal, and as preloads. Studies were excluded if they: 1)