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Review

Metabolic effects of non-nutritive sweeteners

M. Yanina Pepino *

Center for Human Nutrition, Washington University School of Medicine, St. Louis, MO, United States

HIGHLIGHTS

- NNS use in humans is linked to weight gain and type 2 diabetes risk.
- NNS in rodents disrupt learned responses that help control glucose homeostasis.
- NNS in rodents alterglycemic responses to a sugar load by perturbing gut microbiota.
- NNS increase intestinal glucose transporter expression in three mammalian species.

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ABSTRACT

Until recently, the general belief was that non-nutritive sweeteners (NNSs) were healthy sugar substitutes because they provide sweet taste without calories or glycemic effects. However, data from several epidemiological studies have found that consumption of NNSs, mainly in diet sodas, is associated with increased risk to develop obesity, metabolic syndrome, and type 2 diabetes. The main purpose of this article is to review recent scientific evidence supporting potential mechanisms that explain how "metabolically inactive" NNSs, which have few, if any, calories, might promote metabolic dysregulation. Three potential mechanisms, which are not mutually exclusive, are presented: 1) NNSs interfere with learned responses that contribute to control glucose and energy homeostasis, 2) NNSs interfere with gut microbiota and induce glucose intolerance, and 3) NNSs interact with sweet-taste receptors expressed throughout the digestive system that play a role in glucose absorption and trigger insulin secretion. In addition, recent findings from our laboratory showing an association between individual taste sensitivity to detect sucralose and sucralose's acute effects on metabolic response to an oral glucose load are reported. Taken as a whole, data support the notion that NNSs have metabolic effects. More research is needed to elucidate the mechanisms by which NNSs may drive metabolic dysregulation and better understand potential effects of these commonly used food additives.

Contents

* Center for Human Nutrition, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, United States.
E-mail address: ypepino@dom.wustl.edu.

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1. Introduction

It is generally believed that non-nutritive sweeteners (NNSs) are healthy substitutes for sugars because they provide sweet taste without calories or glycemic effects [1]. Currently, six NNSs (sucralose, aspartame, saccharin, acesulfame potassium, neotame and advantame) are approved to be used as a sweetener in food, and two (steviol glycosides, and Luo han guo extract) are generally recognized as safe and permitted for use in food by the US Food and Drug Administration (FDA) [2]. Although these compounds have very different chemical structures, they all have in common the ability to very potently activate some of the multiple potential ligand binding sites of the heterodimeric T1R1 + T1R3 sweet-taste receptor in human subjects [3]. Before the FDA granted final approval of NNSs, a battery of toxicology and clinical studies in a number of species, including humans, were conducted to demonstrate that NNSs are generally safe and well-tolerated. In addition, the data from several studies, conducted in human subjects with and without diabetes, found that even extremely high doses of sucralose or aspartame (many times above the estimated maximum intake), did not affect blood glucose, C-peptide, or HbA1c concentrations (e.g., [1,4–6]). However, data from several epidemiological studies have found that consumption of NNSs, mainly in diet sodas, is not linked to better health outcomes (reviewed in [7,8]). In fact, some studies found positive associations between NNS consumption and weight gain, metabolic syndrome, and type 2 diabetes [9–14], although other studies did not (e.g., [15,16]; reviewed in [17]).

At least two hypotheses, not mutually exclusive, might explain the paradoxical association between consuming NNSs and adverse metabolic outcomes: 1) reverse causation, i.e. individuals who are likely to develop metabolic disease or are gaining weight choose to consume NNSs as a strategy to reduce sugar and caloric intake; and 2) NNSs are not physiologically inert but affect biological processes involved in regulating energy and glucose homeostasis. This article reviews recent scientific evidence supporting potential mechanisms that explain how "metabolically inactive" NNSs, which have few, if any, calories, might promote metabolic dysregulation and presents some findings from our laboratory in which we explore associations between individual taste sensitivity to detect sucralose and sucralose acute effects on metabolic response to an oral glucose load.

2. Potential mechanisms underlying the association between the use of nonnutritive sweeteners and adverse metabolic outcomes

The list of potential mechanisms described below is not collectively exhaustive, nor mutually exclusive. In fact some of these mechanisms may act synergistically.

2.1. NNSs interfere with learned responses that contribute to control glucose and energy homeostasis

Much of the evidence behind this concept derives from the seminal work by Swithers and Davidson in a rodent model ([8,18–20], reviewed in [21]). Using the Pavlovian conditioning principles as the foundational context of their research, they hypothesize that the use of NNSs weakens the ability of sweet taste to predict energy and evoke autonomic and endocrine learned responses that prepare the digestive tract for the optimal process of ingested food, such as the cephalic response [19]. In their elegant animal model, rats receive differential experience with a sweet taste that either predicts (glucose) or does not predict (saccharine, acesulfame K, or stevia) increased calories. Data from a series of experiments show that compared with rats that consume a diet always sweetened with glucose (i.e. sweet predicts calories), those consuming a diet where sweet taste does not reliably predict calories (i.e. sweetened with NNSs) are heavier, accumulate more body fat, exhibit a diminished ability to compensate for calories ingested in a pre-meal, and have a reduced thermic response to eating a novel meal [18,19,22,23]. Consistent with their hypothesis that NNSs weaken cephalic responses, compared with rats in the control group (i.e. sweet predicts calories), animals consuming a diet sweetened with NNSs responded with relative hyperglycemia when given a novel sweet-tasting test meal or a standard glucose tolerance test [24]. Importantly, this altered glucoregulatory response to a glucose load, which was associated with reduced circulating levels of the incretin hormone glucagon like peptide-1 (GLP-1), was observed when the glucose load was given orally but not when glucose was infused directly into the stomach by gavage (i.e. bypassing oral taste stimulation) [24]. That previous experience with NNSs affected glucoregulatory responses to a glucose load when glucose was tasted, but not when directly released in the stomach, further supports their hypothesis that it is disruptions in learned responses elicited by tasting sweetness, not in post-absorptive consequences of consuming sugar, that alter glucose homeostasis in this rodent model.

Early studies by Deutsch [25] also strongly support the theory that in rodents, long-term exposure to NNS ingestion weakens cephalic responses triggered by sweet taste. Following up from findings that saccharin ingestion potentiated hypoglycemic effects of exogenous administered insulin [26], Robert Deutsch tested the hypothesis that the sweet taste of saccharin elicited a conditioned hypoglycemic response that could be extinguished by giving animals long-term access to the non-caloric sweetener [25]. He showed that, consistent with the conditioning theory, saccharin ingestion alone leads to relative hypoglycemia in animals with little to no prior experience with NNSs. However, such a conditioned hypoglycemic response was extinguished after animals had long-term access to saccharin (i.e. the experience of tasting sweetness without the subsequent rise in blood sugar) [25].

The hypothesis that exposure to NNSs weakens cephalic responses to sweet food has not been tested in human subjects, and future research in this area is warranted. There are important differences between humans and rodents on the type of stimuli that elicit cephalic responses. Sweet liquids, either caloric or non-caloric, are good stimuli to elicit cephalic responses in rats [27–29] but generally do not elicit cephalic responses in human subjects [30–32]. However, given that 1) classical or Pavlovian conditioning is one of the most basic forms of learning (demonstrated even in invertebrates such as the *Aplysia*) [33], 2) cephalic responses are elicited when people taste and chew food ([34], reviewed in [35]), and 3) studies in human subjects show that cephalic responses are required for a normal postprandial glucose tolerance [36,37], there is great potential that the above theory, which posits that NNSs interfere with learned responses that contribute to control glucose and energy homeostasis, is applicable to human subjects.

2.2. NNSs interfere with gut microbiota and induce glucose intolerance

Perhaps the one unquestionable benefit of NNSs is that they help reduce dental cavities [38]. The anticavity effect of saccharin, sucralose, aspartame, and stevia is not only explained by the fact that these compounds are resistant to fermentation by oral bacteria, but also because of their demonstrated bacteriostatic effects [39–41]. Data from studies in vitro [42] and in animal models [43–45], and from a small study in human subjects [45], suggest that the effects of these NNSs are not limited to the microbial inhabitants of the mouth, but extend to those in the gut, thereby affecting the host metabolic phenotype and disease risk [46]. Pioneer work from the group of Schiffman showed that 12 weeks of exposure to Splenda (a NNS comprising 1% *w*/*w* sucralose with glucose (1% *w*/*w*) and maltodextrin (94% *w*/*w*) as fillers) significantly altered gut microbiota composition by decreasing beneficial bacteria and was associated with weight gain in rats [43]. In a recent work, Suez et al. confirmed and extend these findings by identifying a microbe-mediated mechanism by which NNSs might influence metabolism [45]. Suez et al. showed that 11 weeks of exposure to saccharin, sucralose, or aspartame