

Sugar substitutes: deep dive into the pros, cons, available options, and impact on metabolic health

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Sweet receptor multiple binding sites

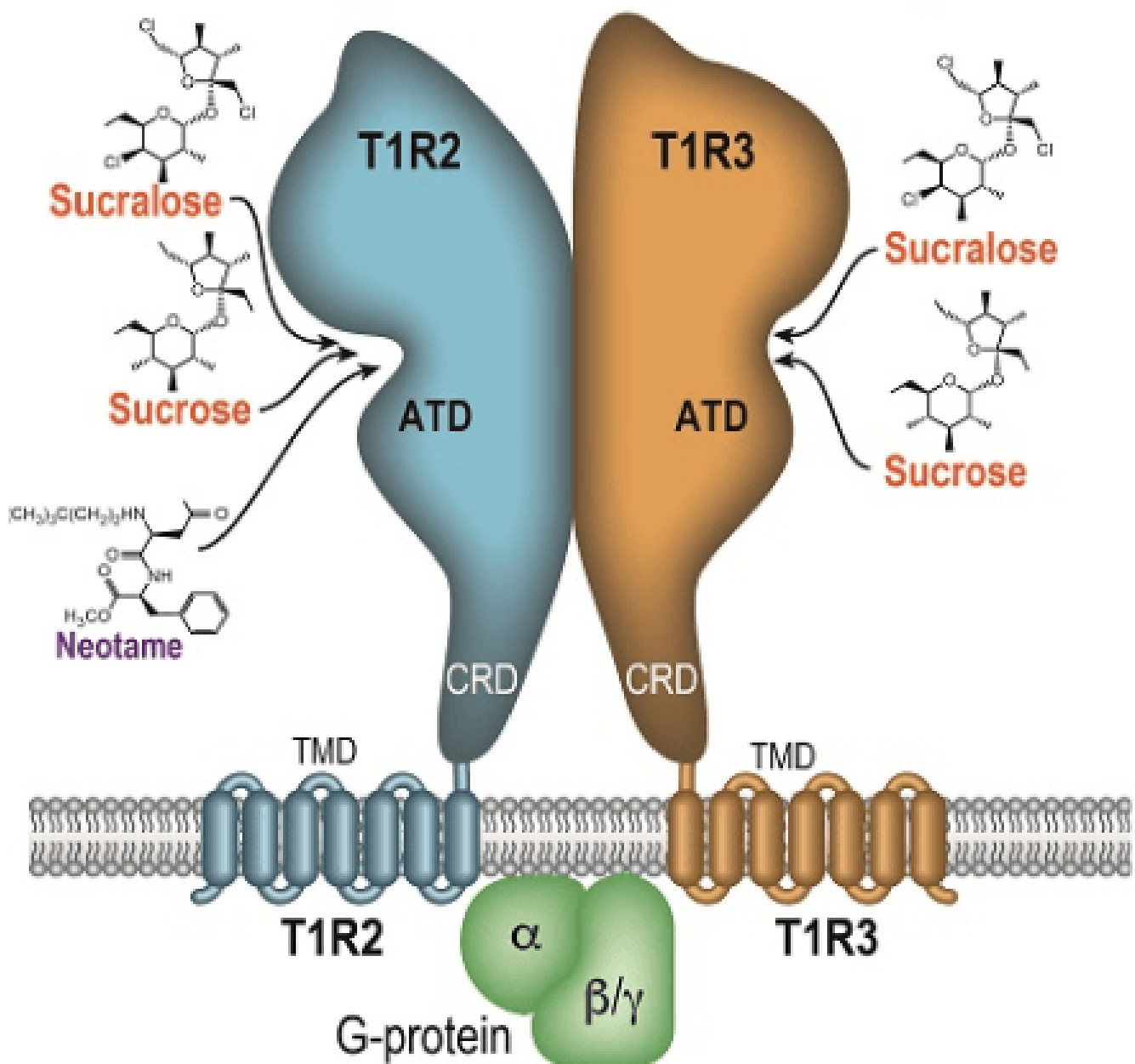


Figure: Schematic representation of the oral sweet taste receptor. The receptor is a dimer of two G-protein-coupled receptors, T1R2 and T1R3, and contains multiple sites for binding sugars and sugar substitute compounds. Adapted from [Assadi-Porter et al.](#), *Molecules*, 2018.

We've all heard that sugar is bad for us. Long-term, high levels of sugar consumption – in the form of sucrose (i.e., table sugar), high fructose corn syrup, or otherwise – can lead to weight gain and elevated risk for many of the most deadly chronic diseases, including metabolic

syndrome and type 2 diabetes, cardiovascular disease, liver disease, Alzheimer's disease and dementia, and certain types of cancer.

And yet, it's hard to deny sugar's appeal (and its ubiquitous presence in Western food environments as a result). Although some may have a stronger sweet tooth than others, all humans are born with a [predisposition](#) to enjoy and seek out sweet tastes. This preference is [hardwired](#) in the mammalian brain and thus can't be "unlearned," and, as [Dr. Rick Johnson](#) has previously discussed on the podcast, it likely served as an advantage during human evolution.

So now we have a substance that accelerates disease and mortality, and a substance that is highly-rewarding and holds universal, innate appeal. Two sides of the same sugar-coated coin. But what if we could separate the enjoyable qualities from the health concerns?

Cue the rise of artificial/non-nutritive sweeteners and other sugar substitutes, a class of compounds that provide sweet taste but few or no calories. Theoretically, they offer the best aspects of sugar with none of the downsides, but of course, the story is not that simple. While these compounds remain popular, they are controversial and certainly haven't made excessive sugar consumption a concern of the past. So how well do these substitutes solve the problems associated with traditional sugar, and where do they fall short? And how do different options compare with each other?

The Science of Sugar Substitutes

We detect sweetness when sugar molecules bind to and activate sweet taste receptors T1R2 and T1R3 on the tongue, triggering neural signals leading to the perception of "sweet." These receptors, which have multiple binding sites (see figure below) can be activated by sucrose (a combination of the simple sugars glucose and fructose), by other sugars (including individual molecules of glucose and fructose), and by sugar substitute compounds. Indeed, many sugar substitutes bind these receptors even more strongly and tightly than sucrose does, and they are thus perceived as being sweeter, in some cases by as much as 2-3 orders of magnitude (100-1,000x more), which allows us to use less to achieve the same level of sweetness (see table 1 for a comparison across the most common sugar substitute compounds).

Sweet receptor multiple binding sites

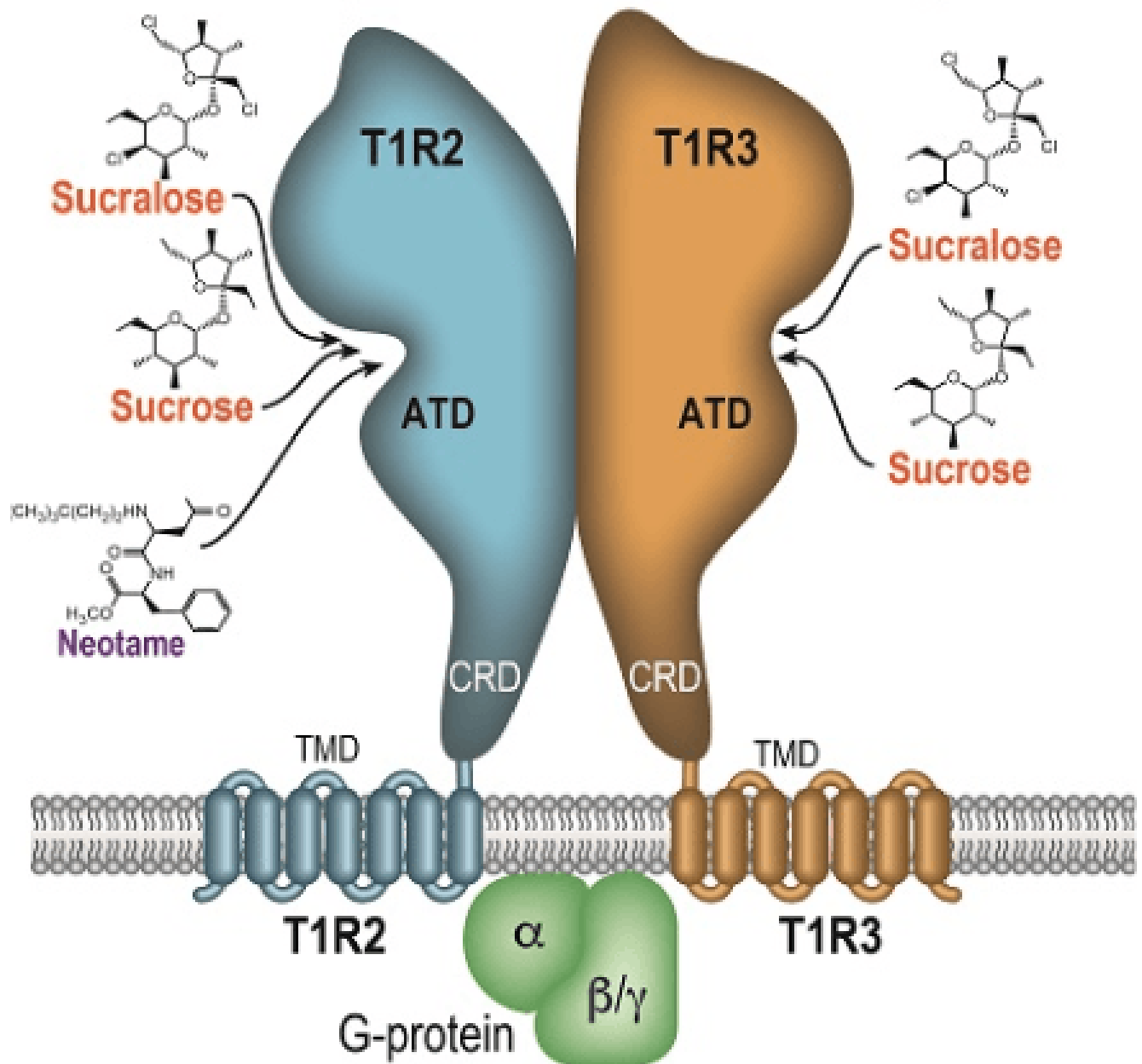


Figure: Schematic representation of the oral sweet taste receptor. The receptor is a dimer of two G-protein-coupled receptors, T1R2 and T1R3, and contains multiple sites for binding sugars and sugar substitute compounds. Adapted from [Assadi-Porter et al.](#), *Molecules*, 2018.

Table 1: Relative sweetness and caloric values of common sugar substitutes

Compound	FDA Approval Date	Trade Name(s)	Sweetness*	Calories (kcal/gram)
Sucrose	N/A	Many (table sugar)	1.0	4.0
Saccharin	1958**	Sweet'n Low	300	0.0
Xylitol	1963	XyloSweet, others	1.0	2.4
Aspartame	1981	NutraSweet, Equal	180-200	4.0
Acesulfame potassium (Ace-K)	1988	Sweet One, Sunett	200	0.0
Sucralose	1998	Splenda	600	0.0
Erythritol	2001	Zerose	0.7	0.2
Steviol glycosides/ Stevia extracts	2008	Truvia, PureVia, SweetLeaf	100-300	0.0
Allulose	2012	Dolcia Prima, others	0.7	0.2

* Relative to a 10% sucrose solution

** Use of saccharin dates to the 1890s, prior to oversight by the FDA with the Food Additives Amendment of 1958.

Although we *taste* the sweetness of sugar substitutes in the same way that we taste the sweetness of sucrose, we do not *metabolize* these compounds in the same way. The components of sucrose are absorbed from the gut and metabolized by the liver and other tissues to provide energy (i.e., calories). Zero-calorie sweeteners, in contrast, are either not absorbed or are absorbed but then excreted without generating energy for the body. Additionally, some sugar substitutes are considered “low calorie” because they are only partially absorbed or metabolized, thus providing fewer calories than equivalent quantities of sucrose. One noteworthy exception is aspartame, which, gram for gram, provides the same number of calories as sucrose, though it is metabolized by alternative pathways. However, because aspartame is 200x sweeter than sucrose, it is still considered “low calorie” by virtue of the fact that it is used in much smaller quantities than sucrose. (Like all sweeteners that are many times sweeter than sucrose, most of what you pour out of the little blue or pink or yellow packet is not the active ingredient but instead an inert filler. This filler brings the sweetness-per-volume to roughly that of sucrose, allowing 1:1 substitutions and measurements, though it often alters the product’s texture and mouthfeel.)

The logic is certainly sound: sweeter taste, fewer calories. So why do sugar substitutes remain such a subject of debate?

Why are they so controversial?

The use of sugar substitutes is usually driven by a desire to improve or maintain body weight and/or glycemic control by reducing calorie intake (and specifically, calories from sugar) while still satisfying one's sweet tooth. Yet the efficacy of non-nutritive sweeteners in accomplishing even these most basic and fundamental purposes is probably the single most hotly debated subject with respect to these products. This question has been the subject of decades' worth of research and a colossal body of scientific literature, but the answers that have emerged are far from straightforward and universally agreed upon.

In large part, this is because investigations on sugar substitutes suffer from many of the same obstacles and pitfalls as any other nutrition research. Randomized controlled trials (RCTs) are costly and generally not of long enough duration to see meaningful differences between groups. Further, the ubiquity of both sugar and sugar substitutes in everything from condiments to cough syrups creates extraordinary challenges for controlling such studies and ensuring compliance. This problem also undermines the accuracy of self-reported sweetener intake in epidemiological studies, which, in addition, are subject to significant confounds from socioeconomic status, healthy user bias, and other sources.

Much of what we know about the effects of sugar substitutes comes from animal studies, but these too have many noteworthy limitations. For instance, laboratory animals have limited control over their eating habits and are not informed (as humans typically are) about whether they are consuming sucrose or a zero-calorie alternative – a knowledge which could easily impact behavior.

Additionally, although sugar substitutes are a heterogeneous group of compounds, many studies and meta-analyses lump them together with little or no regard to variability in results across different products. Certain effects of sugar substitutes are indeed likely to be common to all – such as those related to their unifying mechanism of dissociating sweet taste and calorie intake – but others – such as those related to how these compounds are metabolized – cannot be generalized so readily.

Despite these shortcomings, we have done our best in the text below to evaluate existing evidence for and against the efficacy of sugar substitutes as a general group, followed by any noteworthy considerations for common sweeteners individually.

Efficacy vs. Effectiveness

Before we dive in, let's start by making the important distinction between *efficacy* and *effectiveness*, particularly as they relate to the subject of sugar substitutes. *Efficacy* refers to how well a given intervention “works” under controlled conditions in which all participants adhere to the treatment perfectly, while *effectiveness* refers to how well an intervention “works” under natural conditions in which people are free to make their own choices about compliance and other lifestyle factors. These concepts should not be confused with the interventional

versus observational studies; both efficacy and effectiveness can be assessed using randomized trials of different designs, each with their own limitations in terms of control and generalizability.

With respect to sugar substitutes, we can ask two types of efficacy questions: (1) how do low-calorie sweeteners affect the outcome of interest when sweetener and sucrose groups are consuming the same total number of calories? The sweetener group in this case would eat more non-sugar calories than the sucrose group to match total calories. And (2) how do low-calorie sweeteners affect the outcome of interest when sweetener and sucrose groups' diet composition differs only in whether they are consuming sweetener or sucrose? In this case, the sucrose group would consume more total calories than the sweetener group, with the excess coming solely from sucrose. These two types of efficacy trials are interesting from the perspective of health (e.g., inflammation, insulin sensitivity, etc.) but less so from the perspective of energy balance. In essence, these trials ask, "are people consuming these fake sugars, even if losing weight, less healthy?" Or conversely, "under isocaloric conditions, does sucrose consumption have a deleterious impact on health that non-nutritive sweeteners do not?"

Effectiveness trials are where the money is, as these are the trials that investigate what real people can expect in a real-world setting. These trials can determine, for example, if those consuming artificial sweeteners end up eating more elsewhere. Such trials are typically longer than efficacy trials and, by definition, are less controlled.

Keeping in mind the distinction between these concepts is key as we review the data on sugar substitutes and metabolic effects, as it helps to explain some of the variability in results across trial designs and to define limits to the conclusions we can make from any individual study.

Do they help control body weight?

Of the RCTs that have investigated the efficacy of sugar substitutes in promoting weight loss or preventing weight gain, most have been of fairly short duration and small cohort sizes. Still, according to a [2014 meta-analysis](#) reviewing data from 15 RCTs, experimental groups given low- and no-calorie sweeteners generally showed improvements in metrics such as body weight, body mass index (BMI), fat mass, and waist circumference relative to control groups, which were typically advised to continue with a normal diet or were given sugar-sweetened beverages in place of the low-calorie sweetener beverages provided to experimental groups. These improvements were clinically small (for instance, the average body weight reduction across trials was about 1.8 lbs for those on sweeteners) but were statistically significant. A [2020 meta-analysis](#) including 20 RCTs produced similar findings but further reported that results on body weight generally favored non-nutritive sweeteners specifically in subjects with overweight or obesity, as well as when the sweeteners were compared against sucrose (as opposed to an absence of any sweetener). For instance, analysis revealed that in patients with overweight or obesity, non-nutritive sweetener intake resulted in an average loss of 5.6 lbs versus an average loss of 2.9 lbs among controls ($P < 0.001$), whereas studies in normal weight individuals showed no significant differences in body weight changes between sweetener groups and controls.

But observational studies and animal research tell a very different story. The 2014 meta-analysis described above also included a separate review of nine prospective cohort studies, from which the authors report an overall *positive* correlation between low-calorie sweetener consumption and increases in BMI. Changes in body weight also tended to be associated with sugar substitute consumption, though this result did not reach statistical significance. Further, an [analysis](#) of data from the [San Antonio Heart Study](#) showed that the positive relationship between artificial sweetener consumption and weight-related metrics (change in BMI and incidence of overweight/obesity over the 10-year observation period) was dose-dependent (n=3,682), even after adjusting for baseline BMI and other confounding factors such as smoking and exercise habits.

Some animal [studies](#) have shown that sugar substitutes can cause rodents to overeat and consequently gain weight, but interestingly, others suggest that low-calorie sweeteners may induce weight gain even *without* triggering increased total calorie intake. A [study](#) in rats showed that diets sweetened with saccharin or aspartame – but not diets sweetened with sucrose – resulted in weight gain despite comparable total caloric intake across groups. Similarly, a [study](#) in mice found that animals given a saccharin solution gained more weight than controls given water despite consuming approximately 14% *fewer* total calories. (Of note, no weight gain was observed among animals given a sucralose solution, despite statistically equivalent calorie intake between sucralose and saccharin groups.) These data suggest that sweeteners may decrease energy expenditure, which might relate to effects on activity level or basal metabolic rate; however, neither study monitored either of these variables. The results could alternatively be explained by effects on nutrient absorption from the intestine – i.e., sugar substitutes may increase absorption and utilization of ingested calories. Notably, both of these latter studies were much longer in duration than the study observing increased calorie intake with sugar substitutes, so it is possible that sweeteners have a short-term effect on food intake that disappears on longer timescales, perhaps related to a decline in energy expenditure.

Do they help to maintain or improve glycemic control?

RCTs investigating the efficacy of sugar substitutes in improving or maintaining glycemic control have yielded conflicting results, with some reporting modest benefit, others reporting harm, and many reporting no effect. This heterogeneity does not appear to reflect different effects of different sweeteners, as divergent results have been reported for the same compounds across separate studies. Rather, differences in study design details are more likely to account for the variability in results. (For example, a number of studies provide artificial sweeteners in capsule form, thus bypassing oral sweet taste receptors. Though results with this approach generally indicate that non-nutritive sweeteners have no effect on insulin sensitivity or glycemic parameters, these studies do not reflect how humans would normally be consuming these products and therefore offer little meaningful insight for consumers.)

In considering patterns across randomized trials, we see again that the nature of the *control* intervention is a key experimental detail in determining results. When compared to consumption of foods or beverages sweetened with sucrose, consumption of foods and beverages sweetened by low-calorie substitutes has been [reported](#) to [improve](#) metrics related

to glycemic control, such as postprandial glucose, insulin, and incretin responses. In contrast, when control groups are given water or other unsweetened products as a placebo, experimental groups given sugar substitutes tend to exhibit glycemic control that was [poorer than](#) or [comparable to](#) that of controls by the end of the intervention period. Collectively, these results suggest that low- and no-calorie sweeteners have metabolic benefits when used to *replace* sucrose or other calorie-providing sugars that would otherwise have been consumed but may have the opposite effect when used *in addition* to whatever sweeteners or sugars would normally be present in the diet. In other words, for someone who routinely drinks a couple of cans of regular Coca-Cola every day, switching to a couple of cans of Diet Coke might improve metrics of glucose metabolism, but for someone who drinks soda water at baseline instead of Coca-Cola, switching to an artificially sweetened beverage may be harmful.

But again, the picture looks a bit more grim when we examine data from observational and animal studies. A 2021 [meta-analysis](#) of prospective cohort studies assessing the relationship between artificial sweetener consumption and diabetes incidence reported an overall 13% *increase* (95%CI: 1.03-1.25) in type 2 diabetes risk for every additional serving of an artificially sweetened beverage per day. Though heterogeneity across studies was high, risk was found to increase in a dose-dependent manner. Further, a [recent study](#) revealed that rats supplemented with a mix of aspartame and sucralose for 12 weeks exhibited increased hemoglobin A1c (HbA1c) and HOMA-IR (a metric of insulin resistance) at the end of the intervention period relative to both normal-diet controls and to animals supplemented with sucrose.

What might explain the discrepancy in results?

I've long been vocal about my higher regard for randomized trials in humans over either epidemiological studies or data from animals. However, in the case of sugar substitutes, RCTs to date have all had one flaw that raises doubts about their reliability: they've all been very short.

For interventions that rapidly induce effects of large magnitude on body weight or glucose tolerance (for instance, GLP-1 receptor agonist drugs), study durations of a few weeks or months may be enough to see significant differences between controls and intervention groups. But these timelines may not be sufficient to reveal effects of more modest size, as is likely to be the case with any effect (positive or negative) of artificial sweeteners. The development of metabolic disease and obesity through a small elevation in risk may take years or even decades.

In addition to the likelihood that sweeteners have a small effect requiring years to reach significance, they may also have categorically distinct metabolic effects on short versus long timescales. Non-nutritive sweeteners have been shown to modulate the gut microbiome and induce gradual changes in neural signaling. These changes can in turn alter the body's metabolic response to sugar substitutes as well as to natural sugars and other nutrients. In other words, sweeteners may result in metabolic benefits in the short term, but after the brain and body have had time to adjust to the disconnect between sweet taste and calorie load, the net effect shifts in a negative direction. But how?

How do sugar substitutes impact the microbiome?

Research over the last 20 years has heightened appreciation for diverse roles of the microbiome – the community of trillions of bacteria and other microbes dwelling on and within the human body – in human physiology and health. The vast majority of these microbes (>90%) live inside the gastrointestinal tract, mouth to anus, where they interact with the food we consume and exert myriad effects on immune function and inflammation, [crosstalk](#) between the gut and the brain, hormone regulation, and other processes which ultimately appear to impact [risk](#) for a growing number of diseases, including neurodegenerative and metabolic diseases. As these effects depend in large part on the specific microbial species present in the microbiome, much work has been devoted to elucidating the species and patterns that are associated with positive and negative health conditions, including those related to weight gain and development of glucose intolerance.

Humans may not be able to metabolize most sugar substitutes, but these compounds can nevertheless have profound impacts on the microbial communities within us, which in turn can lead to downstream metabolic effects for the human host. Interventional studies in humans linking non-caloric sweetener intake and microbiome changes have been scarce and have yielded mixed [results](#), though a number of studies in lab animals (e.g., [Abou-Donia et al.](#) and [Cowen et al.](#)) have shown that the microbiomes of rodents given artificial sweeteners subsequently shifted in favor of species associated with metabolic and inflammatory diseases. However, these results cannot prove causality, as the microbiome changes were accompanied by the development of glucose intolerance, and the effects on the microbiome could therefore have been caused by the metabolic dysfunction rather than the other way around.

But in 2014, a landmark [study](#) by Suez et al. provided definitive evidence that indeed, non-nutritive sweeteners caused alterations in the mouse microbiome which secondarily drove the development of glucose intolerance. As in previous studies, the authors reported that experimental groups taking artificial sweeteners (specifically, saccharin, aspartame, and sucralose) became glucose intolerant and had altered microbiome compositions, while sucrose- and water-treated control groups did not exhibit either of these effects. However, the investigators found that antibiotic treatment – which destroys the gut microbiome – abolished the effects of sweeteners on glucose tolerance, indicating that effects on glycemic control were caused specifically by the effects on the microbiome.

Suez et al. then conducted an experiment in which “normal” microbiota samples were taken from control mice, cultured *in vitro* in the presence of artificial sweeteners, and transferred to the gastrointestinal tract of mice with no pre-existing microbiome. Remarkably, these “germ-free” mice – which had never been exposed to the sugar substitutes – developed the same glucose intolerance phenotype as mice treated with sweeteners in their diet. By exposing the microbes to the sweeteners only in an *in vitro* setting, the authors thus demonstrated that the changes to the microbiome were a direct result of the sweeteners and not secondary to any other potential physiological effect on the host. In other words, these results – schematically summarized in Figure 2 – indicate that non-nutritive sweeteners can directly alter the species composition of the gut microbiome, and that these changes can subsequently *cause* metabolic derangements.

Of note, the same research group published results last year from a [randomized trial](#) in humans in which they again showed that artificial sweeteners caused disturbances in the gut microbiome and, in the case of certain sweeteners, led to impairments in glycemic control. In the human trial, the investigators did not perform additional tests with antibiotics to demonstrate that effects on glycemic control are a direct result of effects on the microbiome. However, they did transfer microbiome samples from the sweetener-exposed humans to germ-free mice unexposed to sweeteners, and these animals subsequently developed glycemic phenotypes mirroring those of the corresponding humans. These results strongly support the idea that non-nutritive sweeteners cause microbiome changes which in turn cause derangements in glucose metabolism.

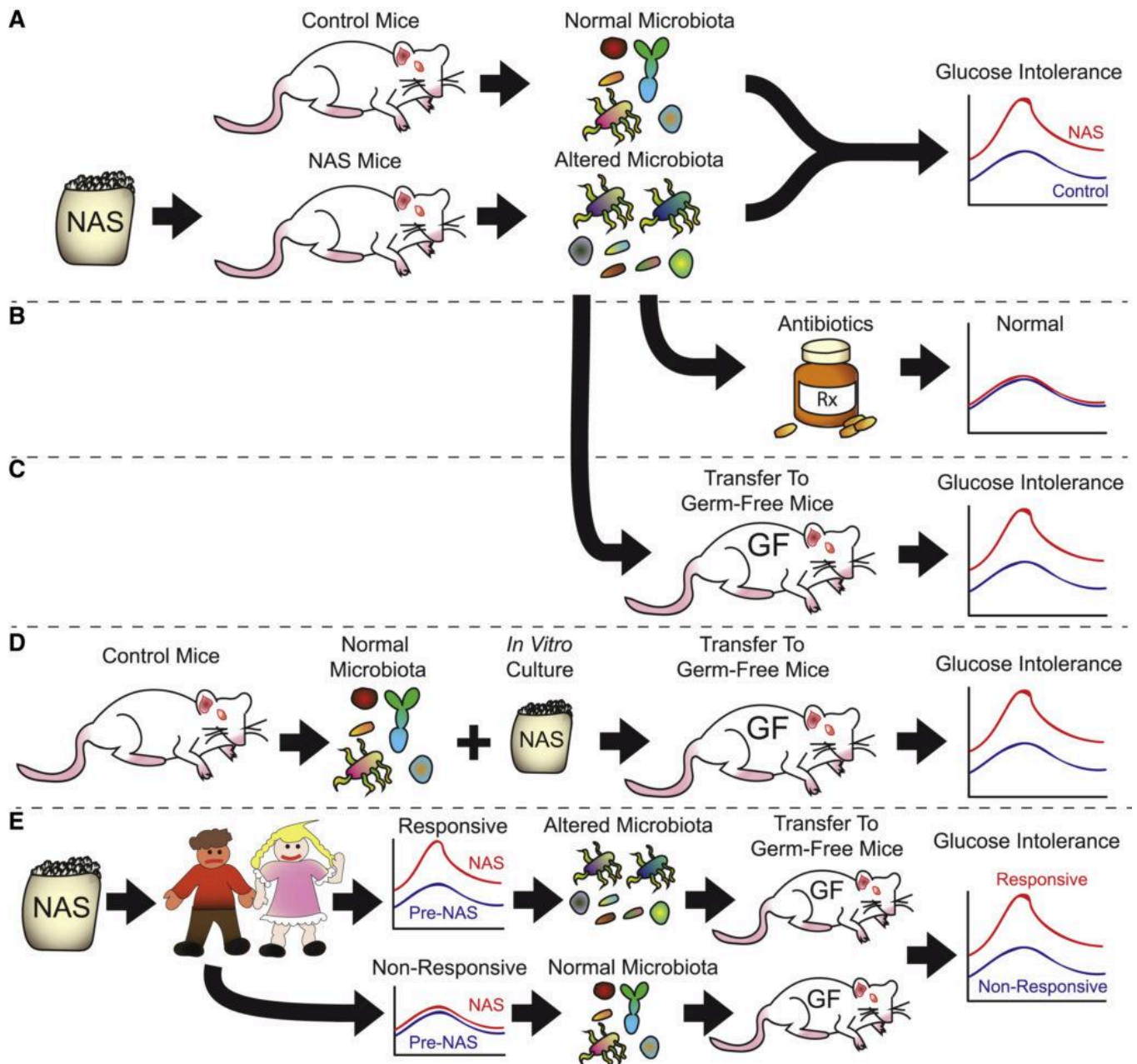


Figure 2: Schematic design and results from [Suez et. al 2014](#). Results demonstrate that non-caloric artificial sweeteners (NAS) alter the gut microbiome and that these alterations result in glucose intolerance. Schematic from [Bokulich & Blaser, 2014](#).

Whether in mice or humans, the diet-induced changes in microbiome species composition tend to be fairly rapid (on the order of [days](#)). But for humans, many of the downstream effects of these changes on host health and metabolism may take months or years to compound to a level that they become measurable or clinically relevant. This presents challenges for studying the long-term implications of sweetener-induced microbiome effects in human populations, as the independent variable of microbial composition is likely to change on far shorter timescales than the dependent variables (metrics of metabolic health). Given our relatively new recognition of the importance of the microbiome, we are still in the early stages of understanding its complex and varied interactions with human hosts, but animal data certainly implicate it as a likely pathway through which sugar substitutes might paradoxically result in metabolic dysfunction.

Effects on the brain: why are low-calorie sweeteners unsatisfying?

Those of you who have tried to replace sugar with low-calorie alternatives might be familiar with another major reason why the substitutes may not be as effective in practice in controlling body weight and metabolic health as we might hope: we just don't find these sweeteners very satisfying.

It's not just you. It has long been clear that non-nutritive sweeteners do not drive intake preferences, motivate consumption, or trigger satiation in the way that sucrose is capable of doing. Human neuroimaging studies have shown that sucralose results in significantly less activation of the brain's reward circuitry than sucrose, and most human [experiments](#) have shown no decrease in hunger or calorie intake among those consuming foods or beverages sweetened with sugar substitutes relative to those consuming foods or beverages sweetened with sucrose or without any added sweetness.

Animal studies, which allow more direct mechanistic investigations, have also established how sucrose – *but not artificial sweeteners* – drive consumption. Mice given a choice between artificially sweetened water and sugar-sweetened water of comparable levels of sweetness have been [shown](#) to consume both at equivalent rates initially, but within 24 hours, they shift toward a striking preference for the sugar-sweetened option. This switch occurs even when animals lack functional T1R2/T1R3 receptors (and are thus incapable of tasting sweetness) and even when a non-metabolizable glucose analogue is [used](#) in place of glucose (or sucrose) itself, indicating that the preference does *not* depend on sugar's caloric value.

So if it isn't about the sweet taste and isn't about the calorie content, what could possibly explain the difference in response to sugar substitutes versus the real deal? Recall that we taste the sweetness of sugar substitutes on the tongue and palate in the same way that we taste the sweetness of sucrose. This is true, but we now know that *post-ingestive* sensation in the gut can differentiate between them in a manner that does not rely on subsequent metabolic breakdown – and that these gut-derived signals are ultimately responsible for the development of sugar preferences.

Although below the level of our conscious perception, cells lining the interior of the small intestine can detect sugar through (at least) two distinct mechanisms: the T1R2/T1R3 receptor also present in cells of the tongue and palate, *and* a glucose transporter known as SGLT1 (sodium-glucose co-transporter 1). While all sweeteners share the ability to bind to T1R2/T1R3 (in both the mouth and gut), SGLT1 is far more specific to glucose. Most artificial sweeteners (and even some caloric sugars, such as fructose) cannot act as SGLT1 substrates, but [recent research](#) has shown that this transporter is critical for the transmission of post-ingestive sugar signals from the gut via direct [neural pathways](#) to regions of the brain involved in driving sugar preference and motivating sugar intake.

In essence, this means that no matter how much we boost the sweetness of foods and beverages with low-calorie sugar substitutes, they will *never* satisfy our innate craving for sugar. And if that is the case, it's easy to imagine how these compounds might paradoxically lead to increased calorie consumption: when food fails to satisfy, we tend to eat more in an attempt to reach that elusive gratification. (Let's say a slice of cake sweetened with sucralose has 300 calories while a slice of "real" cake has 400, but if the sucralose cake doesn't curb our sweet tooth, we might find ourselves reaching for the sugar-filled slice shortly afterward – and suddenly, we've consumed 700 calories instead of satisfying ourselves with the 400-calorie slice in the first place.)

Effects on the brain: how do neural effects impact metabolism?

These differences in post-ingestive sensing and subsequent effects on neural signaling have broader implications than less satisfying foods and beverages. They also impact the body's hormonal responses to meals, which in turn impact satiety as well as downstream metabolic effects.

In response to a calorie load, the gastrointestinal tract releases certain hormones – in particular, GLP-1, GIP, and peptide YY (PYY) – which signal satiety and promote cessation of eating. (This is one of the mechanisms by which GLP-1 receptor agonist drugs such as semaglutide are thought to promote weight loss.) Release of GLP-1, GIP, and PYY can be triggered by [various signals](#) for different macronutrients, but the primary pathway for carbohydrate-induced release is through SGLT1 signaling. Consistent with this fact, GLP-1 and PYY levels in humans [increase](#) in response to a glucose solution but often remain unchanged in response to artificially sweetened solutions, and, as expected, this difference is mirrored by the observation that glucose – but not artificial sweeteners – increases sensations of fullness and satiety relative to equal volumes of water alone.

Another potential consequence of the failure of sugar substitutes to stimulate post-ingestive nutrient sensors is a loss of optimal metabolic response to sucrose and other caloric sweeteners. Have you ever stepped from a stationary surface onto a moving carousel or platform and briefly lost balance, only to recover and find you lose balance again upon stepping back to the stationary surface? This happens because the brain is extraordinarily good at adapting the body's responses to fit what it *expects* is appropriate for a given sensory environment. When the sensory environment changes – say, the stationary ground is suddenly replaced by a moving platform – the previous expectations are no longer accurate, so we falter,

but only until the brain adjusts to the new environment and modulates the body's balance accordingly. Unfortunately for those hoping to lose weight and improve metabolism by using sugar substitutes, the brain likely applies the same adaptation principles when it encounters non-nutritive sweeteners.

Normally when we taste sweetness, the sensation is followed shortly afterward by an influx of glucose. To help the body prepare for the influx and prevent blood glucose levels from spiking too high, the brain uses the sweet taste as an advanced warning. Upon detecting sweetness, the brain directs the body to initiate a variety of preparatory processes collectively known as “cephalic phase responses” (CPRs) including, for instance, the stimulation of gastrointestinal movements and the release of incretin hormones (e.g., GLP-1) and a modest amount of insulin *before* glucose is absorbed and blood sugar starts rising (for more examples, see this [review](#)). These anticipatory processes are thought to serve a number of purposes related to optimizing utilization of ingested nutrients and avoiding dramatic swings in metabolic state, such as excessive blood glucose spikes and drops. In other words, CPRs can be conceptualized as a means by which the brain helps us maintain our *metabolic* balance.

But what happens when sweet taste *doesn't* predict an influx of glucose? If we've never encountered this situation before, the brain responds to the taste by triggering digestive motions and release of metabolic hormones as it usually would. But when no glucose is absorbed, those processes become maladaptive. The pre-release of insulin, for example, results in hypoglycemia – a more acutely dangerous condition than a temporary glucose spike. Other cephalic phase responses, such as activation of gastrointestinal motion or the rise in body temperature, simply come at an energetic cost that is never recouped by a subsequent absorption of nutrients. The body temporarily loses its metabolic balance.

Artificial sweeteners might therefore cause the brain to adopt a more cautious approach in all encounters with sweet tastes, even those associated with caloric sugars, by *dampening* CPRs – in essence, a middle-of-the-road response that is suboptimal for both caloric and non-caloric sweeteners. [Many have proposed](#) that through such a degradation of CPRs, sugar substitutes might ultimately compromise the body's mechanisms for maintaining metabolic homeostasis and regulating energy balance. Unfortunately, experimental study of CPRs – particularly in humans – is extremely challenging for a number of technical reasons, and direct evidence of these hypothesized effects remains elusive. However, we know from animal experiments that CPRs can be [modulated](#) through [learning](#), and rats with prior exposure to artificially-sweetened foods and solutions have been [found](#) to exhibit weaker GLP-1 responses to a glucose load than rats previously exposed to equivalent glucose-sweetened foods and solutions, suggesting a dampening of some (but not all) CPRs as a result of prior experience. Other [work in animals](#) has also demonstrated as proof-of-principle how the loss of cephalic responses may be sufficient to cause metabolic derangements.

Considerations for Specific Sweetener Classes

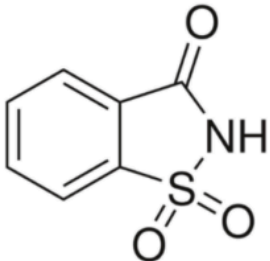
It's important to reiterate that sugar substitutes are a diverse group, with individual compounds differing widely in chemical properties and metabolic fate, so to speak of them under one heterogeneous umbrella is misleading. As such, some sweeteners may differ to some degree

in their effects on body weight and glucose control. Research on the health effects of artificial sweeteners unfortunately has not been evenly divided across different sweetener classes, as most studies have focused on aspartame, sucralose, or saccharin, but by examining these data alongside the more limited data on other sugar substitutes, we can derive certain clues about whether some options might be more effective in their intended health purposes than others.

Additionally, the majority of observational studies do not distinguish between various sweetener compounds, so we must rely primarily on animal data and short-term interventional studies, few of which have conducted direct comparisons across sweeteners. Therefore, we must attempt to make inferences based on separate trials with different methodological details.

In summary, our assessments below should be regarded as our best guesses based on information currently at hand, and we've attempted to point out the areas where gaps in existing data limit our certainty in these conclusions.

Saccharin

Structure	Quick Facts
 <chem>O=C1NC(=O)c2ccccc2S1(=O)=O</chem>	<ul style="list-style-type: none">• Synthetic sweetener developed and commercialized in the late 19th century• Associated with a bitter aftertaste

Saccharin has a troubled [history](#). A synthetic compound first developed in 1879, it was marketed as a sweetener shortly thereafter and grew in popularity as a result of sugar shortages during the world wars and later as a non-caloric sweetener for those looking to control their weight. Yet saccharin’s safety has been questioned since its earliest days. It was granted the designation “generally recognized as safe” with the Food Additives Amendment of 1958, but the status was later revoked by the FDA in 1972 in light of concerns over carcinogenicity in rats at extremely high doses. Though these concerns persisted for decades, data from human studies eventually led the FDA to reverse its earlier decision, declaring saccharin safe for human consumption in 2001. In all, the extended safety debate has contributed to making saccharin one of the most extensively studied sugar substitutes on this list.

Saccharin is found in a variety of diet foods and beverages, though its bitter aftertaste and history of safety concerns has made it a less popular and ubiquitous option than aspartame, sucralose, and others. Humans absorb ingested saccharin from the GI tract at rates of about 85-95%, and most is excreted unmetabolized in urine within ten hours after ingestion.

Most of the information available to date on saccharin's effects on glucose homeostasis come from animal studies. In rats, repeated [exposure](#) to saccharin solutions resulted in decreased glucose tolerance (and diminished GLP-1 responses to glucose) than exposure to glucose solutions. Saccharin was also one of the sweeteners found in [Suez et al. 2014](#) to disrupt the microbiome in mice and subsequently cause glucose intolerance. In the research group's [2022 follow-up](#) study in humans, it likewise caused microbiome changes and was one of the two sweeteners tested to result in impaired glucose control.

In a rare [trial](#) directly comparing metabolic effects of four different low-calorie sweeteners, investigators Higgins and Mattes randomized 154 participants with overweight or obesity to consume 1.25-1.75 L daily of solutions of sucrose, aspartame, saccharin, sucralose, or rebaudioside A (rebA, a steviol glycoside) for 12 weeks. They showed that saccharin was the only sweetener to significantly increase body weight relative to baseline after the intervention period (Figure 3), and the increase was statistically equivalent to an increase observed in a control group consuming sucrose. Interestingly, the weight gain did not appear to be caused by an increase in total energy intake, as saccharin did not alter this metric relative to baseline or relative to other low-calorie sweeteners.

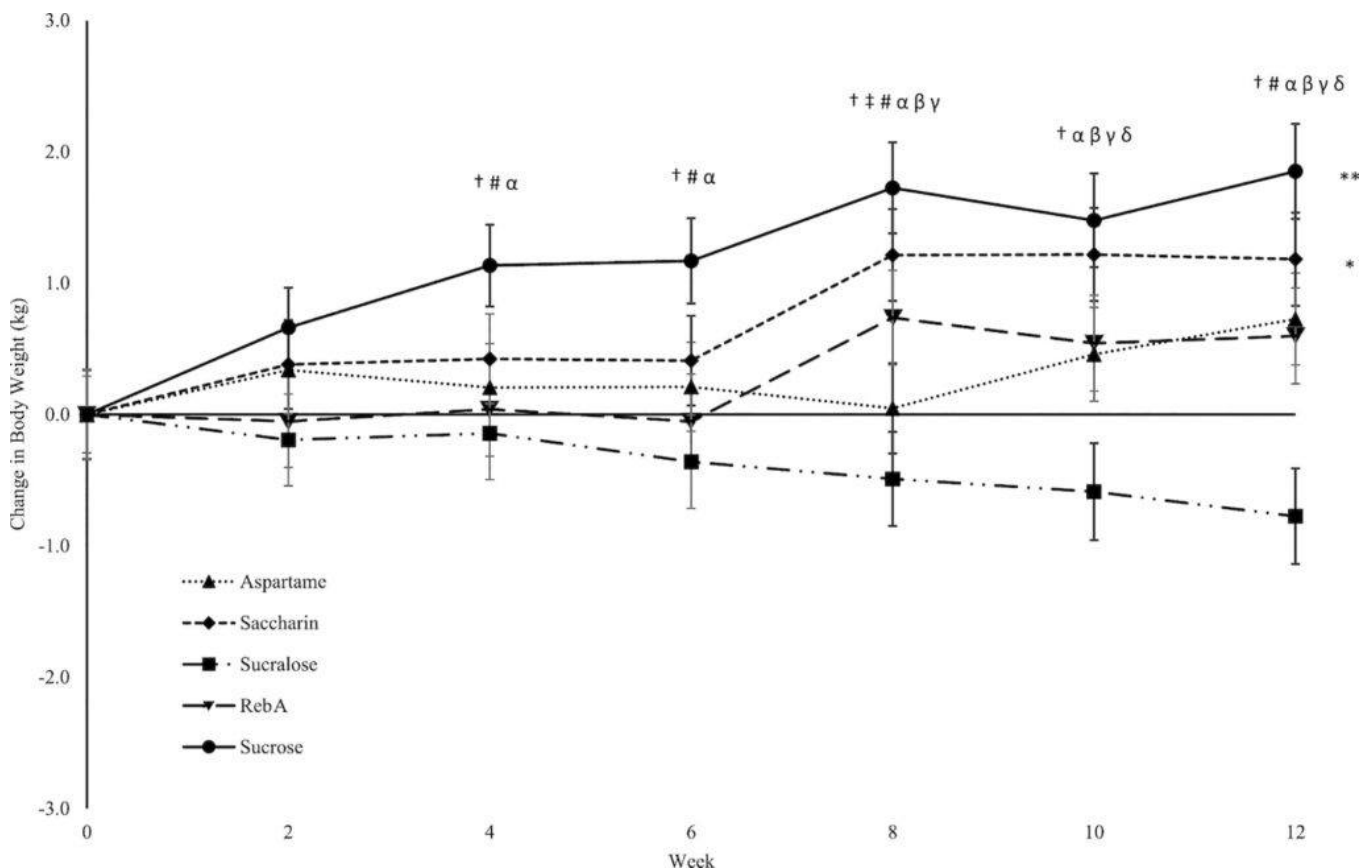
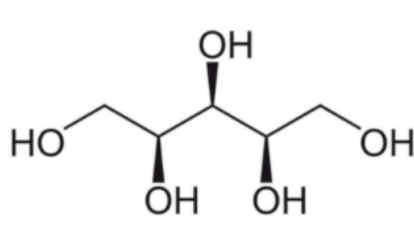


Figure 3: Body weight changes over 12-week treatment with sweeteners or sucrose. Body weight increases relative to baseline were statistically significant for sucrose (** $P < 0.001$) and saccharin (* $P = 0.02$) groups. Symbols above the data points denote significance of between-group comparisons: †, aspartame vs. sucrose; ‡, aspartame significantly different than saccharin ($P < 0.05$); #, rebaudioside A (RebA) sucralose vs. sucrose; α, sucralose vs. sucrose; β, sucralose vs. saccharin; γ, sucralose vs. rebA; δ, sucralose vs. aspartame. (All $P < 0.05$). Source: [Higgins and Mattes 2019](#).

Consistent with these human data, animal studies with saccharin reveal the sweetener to have a detrimental effect on body weight and fat mass, an observation that persists even when saccharin is [compared against](#) caloric sugars. The extra weight gained with saccharin also appears to be sustained after the sweetener is eliminated from the diet, as [rats](#) given saccharin-sweetened yogurt for two weeks gained more weight than rats given glucose-sweetened yogurt, but in the weeks after yogurt was discontinued, the difference in body weights between the two groups did not diminish. While some of these experiments have indicated that weight gain occurs without increased total energy intake (suggesting effects on energy expenditure), others have observed saccharin-treated animals to consume more [total calories](#) than animals given caloric sugars.

Xylitol

Structure	Quick Facts
	<ul style="list-style-type: none"> • Naturally occurring compound in small amounts in many plants, first discovered in 1891 • In the polyol (sugar alcohol) family of sweeteners • Converted to glucose after absorption • Commonly used in sugar-free chewing gum

Xylitol, a member of the sugar alcohol family, is a naturally occurring sweetener found in many plants, including several fruits and vegetables. Humans also produce minimal quantities of xylitol endogenously during the metabolism of glucose. However, because the compound is present only in low quantities in natural sources, chemical production methods are employed for most commercial uses. These uses include sweetening sugar-free candy and dietary supplements, as well as sugar-free gum, particularly in light of xylitol's [well-documented](#) protective effect against tooth decay.

Reported rates of xylitol absorption vary widely and are likely influenced by other dietary and digestive variables, but in most cases, absorption is regarded as >50%. Most absorbed xylitol is believed to be metabolized in the liver to produce glucose or glycogen, partially due to [findings](#) that ingestion of the sweetener does not significantly raise circulating levels of xylitol – but *does* raise circulating levels of glucose. This conclusion is corroborated by the absence of xylitol excretion in urine within 24 hours post-ingestion. Due to its ultimate conversion to glucose, xylitol provides 2.4 calories per gram, and because xylitol must be used in equivalent volumes to sucrose to achieve the same sweetness, this caloric value can contribute significantly to total daily calorie load.

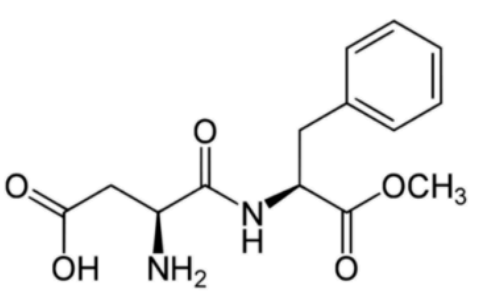
Despite this conversion to glucose, the limited data available – primarily from animal models – indicate that xylitol does not negatively impact glycemic control or insulin sensitivity. For instance, a [3-week study](#) in non-diabetic rats demonstrated that treatment with a xylitol solution resulted in improved glucose tolerance and comparable circulating insulin and lipid levels

relative to both a sucrose solution and water. In a [5-week study](#) of rats with existing diabetes, a xylitol solution was similarly found to result in reduced blood glucose and insulin levels, as well as improved glucose tolerance relative to normal drinking water. However, it bears note that in both studies, the xylitol groups also consumed fewer total calories than either the sucrose or water groups and ended the study with significantly lower average body weight, and these differences may have been responsible for evidently positive effects of xylitol on metabolic metrics.

These results in rats are also some of the only direct evidence to date of xylitol's effects on body weight and appetite, though a handful of small studies in humans provide additional clues. In a placebo-controlled, [randomized trial](#) of 12 healthy, lean participants, infusion of xylitol solutions stimulated dose-dependent secretion of GLP-1, PYY, and cholecystokinin (CCK), another gastrointestinal hormone associated with appetite suppression. However, xylitol was administered intragastrically, leaving an open question about the impact of taste perception on these results. Further, the study did not include a sucrose or glucose control, so it's unclear how GI hormone secretion compares to that stimulated by nutritive sugars and whether it is of sufficient magnitude to make a meaningful difference in food intake. For instance, in a crossover [trial](#) in which participants consumed either a xylitol-sweetened or sucrose-sweetened yogurt prior to a test meal every day for ten days, differences in total energy intake and perceived satiation were not significant between the xylitol and sucrose groups, though results showed trends toward increased satiation and decreased energy intake with the xylitol yogurt.

While these studies offer some hopeful insights, it's worth reiterating that short- and long-term data on artificial sweeteners have often conflicted, so more longitudinal investigations are needed in order to grasp more fully the impact of xylitol on metabolic health. Animal models further support the idea that this sweetener may be a better option for weight management and glycemic control than some others on this list, but because xylitol is ultimately metabolized rather than excreted intact, it also carries a higher potential for unforeseen physiological effects.

Aspartame

Structure	Quick Facts
 The chemical structure of Aspartame is shown. It consists of a benzyl group (a benzene ring attached to a CH2 group) connected to an aspartic acid derivative. The aspartic acid part has a central carbon atom bonded to a hydrogen atom (H), an amino group (NH2), a carboxylic acid group (COOH), and a carbonyl group (C=O) that is part of an amide linkage to the benzyl group. The full structure is: <chem>CC(=O)N[C@@H](Cc1ccccc1)C(=O)O</chem>	<ul style="list-style-type: none">• Synthetic sweetener developed in 1965• Fully metabolized by the human body• The primary sweetener in nearly all major diet sodas

Aspartame is a synthetic sweetener developed by accident in 1965 during research for the development of an anti-ulcer medication. Approved as a food additive by the FDA in 1981, it has since become one of the most ubiquitous low-calorie sweeteners in existence today. Though used in many food and beverage products, aspartame is most notable as the primary sweetener in nearly all major [diet sodas](#).

Unlike most sweeteners listed here, aspartame is fully digested and [metabolized](#) by the human body and yields as many calories, gram for gram, as sucrose, though it is used in much smaller amounts. Aspartame is broken down by digestive enzymes within the GI tract into its component parts – methanol, and the amino acids phenylalanine and aspartic acid – all of which are absorbed and enter circulation. Methanol is metabolized by the liver, while the amino acids are utilized for protein synthesis, with any excess being metabolized or excreted through the kidneys as they would be from any other protein source. (Of note: aspartame's digestion to phenylalanine is the reason why patients with [phenylketonuria](#) are advised against diet soda consumption.)

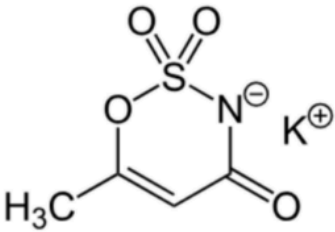
In light of its widespread use, human data on aspartame are abundant compared to most other sweeteners, but effects on glycemic control, body weight, and adiposity are difficult to discern despite the relatively large body of research. Randomized trials involving repeated doses of aspartame have not indicated that the sweetener has any effect on metrics of glucose metabolism and insulin sensitivity, such as HOMA-IR, hemoglobin A1c, or glucose and insulin responses to glucose tolerance tests. These results have been consistent across studies involving participants [with](#) and [without](#) type 2 diabetes (see also [Ahmad et al.](#)). Another [study](#) reporting no effect of aspartame on glucose tolerance additionally observed no differences in appetite, body weight, or GLP-1 or GIP concentrations (during glucose tolerance tests) after 12 weeks of daily consumption of an aspartame-sweetened beverage relative to an unsweetened control beverage. A 1990 [trial](#) even showed aspartame-sweetened beverages to have significant *positive* effects on reducing body weight and limiting energy intake, but this was relative to beverages sweetened with high-fructose corn syrup, a substance notorious for its role in fueling the obesity epidemic. Another [trial](#) reported that water and aspartame-sweetened cola resulted in comparable changes in fat mass after 6 months.

However, observational and animal data have generally conflicted with these positive or neutral results. For instance, in a [2023 report](#) on the NutriNet-Santé cohort, aspartame consumption was associated with a 63% increase in type 2 diabetes risk relative to nonconsumers (95% CI: 1.38-1.93, $P<0.001$). Further, aspartame was one of the sweeteners found in [Suez et al. 2014](#) to cause glucose intolerance via changes to the microbiome in mice, as well as causing gut microbiome changes in their 2022 follow-up in humans, though in the latter case, these changes were not accompanied by a decline in glucose tolerance. A [meta-analysis](#) of prospective studies on body weight and adiposity reported that low-calorie sweetened beverage consumption (which, in most cases, specified aspartame) was positively correlated with increases in body weight and BMI. In animal studies, the sweetener has consistently been found to cause weight gain, [increased fat mass](#), and [fat accumulation](#) in the liver, even when [compared](#) with [sucrose](#)-sweetened alternatives.

As with xylitol, we also need to consider that aspartame is fully metabolized after ingestion, raising the chance that its metabolites might exert various unique effects throughout the body. Animal research has raised concerns over potential [toxicity](#) to the liver, kidney, [brain](#), and most recently, concerns have arisen regarding aspartame and cancer due to a recent [announcement](#) from the World Health Organization. However, these animal studies involved doses far exceeding human consumption levels, and given the components produced by aspartame metabolism, the possibility of toxicity at normal intake levels seems biologically unlikely. The amino acids phenylalanine and aspartic acid are found in every dietary protein source, and we have no evidence that these amino acids would be toxic to those who do not have rare susceptibilities such as phenylketonuria. Although methanol can be acutely toxic at high enough volumes, the amount derived from aspartame-sweetened products is very [low](#) even in comparison to the methanol present in many other foods and beverages, including many fruits and vegetables. (As explained in a recent [newsletter](#), the fears over carcinogenicity are also largely unfounded.)

In all, evidence for acute or chronic toxicity is unconvincing at best, but the most important considerations in deciding whether or not to consume aspartame are its effects on metabolic health. Data suggest that aspartame has equivocal effects on glucose metabolism and likely net negative effects on body weight.

Acesulfame Potassium (Ace-K)

Structure	Quick Facts
	<ul style="list-style-type: none">• Synthetic sweetener first developed in 1967• Known for having a bitter aftertaste and is therefore commonly paired with other sweeteners• Found in many diet sodas (with aspartame)

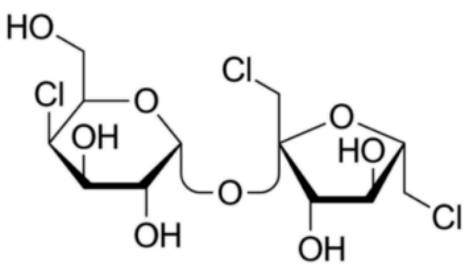
Acesulfame potassium (ace-K) is a synthetic sugar substitute commonly used in combination with other sweeteners to mask its bitter aftertaste. Discovered by accident in 1967, ace-K has been FDA-approved as a food additive since 1988. It is found in many diet food and beverage products, including several diet sodas (e.g., Coke Zero, Diet Pepsi) in which it is typically paired with aspartame.

Nearly all ingested ace-K is rapidly absorbed from the GI tract and enters circulation. Numerous studies in humans and animals have demonstrated that the sweetener does not undergo any metabolism prior to excretion, which occurs primarily through urination. However, because ace-K is a potassium salt, it may dissolve after absorption into separate acesulfame ions and potassium ions. The extent of dissolution isn't known, and studies investigating ace-K excretion have not specified whether the excreted compound is fully intact or in an ion form, but [some](#) have pointed out that the possibility of dissolution makes ace-K a potential source of dietary potassium, an important consideration for those on potassium-restricted diets.

Randomized trials have generally shown ace-K to have no effect on body weight or metrics of insulin sensitivity and glycemic control, though it's worth noting that most of these studies have examined the effects of ace-K in combination with aspartame (see this [recent review](#)), and few have investigated ace-K alone. Epidemiological results, however, indicate an increase in metabolic risk. A recent [publication](#) from the NutriNet-Sante prospective cohort study reported that ace-K was associated with a 70% increase in risk of type 2 diabetes relative to those who do not consume artificial sweeteners (HR 1.70; 95% CI: 1.42–2.04, $P < 0.001$).

In contrast to many other sweeteners commonly used in animal studies, ace-K does not [appear](#) to induce weight gain in mice, though some [evidence](#) suggests the existence of a sex-specific effect, with males more susceptible to ace-K-induced weight gain than females. In rats – which tend to be a better model of human metabolism than mice – ace-K-sweetened food for a period of two weeks was [reported](#) to result in increased total calorie consumption and greater weight gain than foods sweetened with either sucrose or glucose. Results from these and human studies are far from conclusive with regard to the potential harm of ace-K on glucose metabolism and body weight, but it bears note that we have virtually no evidence that ace-K provides any net *benefit* on these aspects of health, in contrast with some of the other sweeteners in this list.

Sucralose

Structure	Quick Facts
	<ul style="list-style-type: none"> • Synthetic sweetener first developed in 1976 • A disaccharide structurally similar to sucrose • Commonly used for diet frozen and baked foods due to broad thermal stability

Sucralose was first synthesized as a derivative of sucrose in 1976 and received limited FDA approval in 1998, followed by approval for use as a general sweetener the next year. Compared to most synthetic sweeteners, sucralose is [stable](#) over a relatively broad temperature range, permitting its use in frozen foods as well as in baked goods or other foods requiring high-temperature cooking.

Most ingested sucralose is excreted in feces, indicating low rates of [absorption](#) from the GI tract, on the order of 10-30%. Of the relatively small amount that reaches circulation, most is excreted in urine without undergoing metabolism.

Much of the evidence (cited earlier) indicating that artificial sweeteners *decrease* insulin sensitivity and glucose tolerance comes from trials involving sucralose, though a few studies have reported sucralose to have a neutral (e.g., [Baird et al.](#)) or positive effect (e.g., [Reyna et al.](#)) on readouts of glycemic control. Again, study design likely plays a large role (for instance, in the Reyna et al. study, the sucralose group's diet also consisted of less fat and fewer total

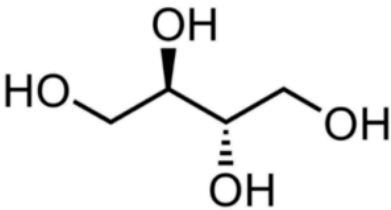
calories than control diets), but the preponderance of evidence from repeated-dose studies appears to tip in favor of a negative effect. Notably, sucralose was also one of the sweeteners found in [Suez et al. 2014](#) to cause alterations in the microbiome and subsequent glucose intolerance in mice, and it was one of the two sweeteners to result in impaired glucose control in humans in the follow-up study, [Suez et al. 2022](#).

Fewer studies have directly examined how sucralose might contribute to weight loss or gain, though it's worth pointing again to [Higgins & Mattes 2019](#), which showed sucralose consumption to cause modest weight loss relative to baseline after 12 weeks of exposure (Figure 3). Indeed, sucralose was the only sweetener tested in this study that resulted in weight reduction, as well as the only sweetener that resulted in a small but statistically significant reduction in total daily energy intake relative to baseline.

Conversely, animal studies indicate that regular consumption of sucralose can [lead](#) to *increased* body weight and fat mass. Mechanistic [investigations](#) in flies and mice have further demonstrated that chronic sucralose consumption promotes an evolutionarily conserved neural starvation response, driving increased food intake. Human [studies](#) have found that ingestion of sucralose solutions fails to stimulate release of GLP-1 and PYY and does not reduce perceived appetite, and yet, when taken in *combination* with caloric carbohydrates, sucralose appears to [increase](#) GLP-1 secretion. In agreement with a lack of satiety hormone release, a [2021 randomized trial](#) comparing sucrose- and sucralose-sweetened beverages showed that females – but not males – consumed more total calories subsequent meal if they had consumed a sucralose-sweetened drink beforehand than if they consumed a sucrose-sweetened beverage.

Collectively, these findings indicate that sucralose is highly likely to have negative effects on glucose tolerance, perhaps more so than any other sweetener on this list. Further, though effects on body weight are somewhat less consistent, mechanistic studies suggest that sucralose is also likely to diminish satiety in the long term despite potential short-term effects in reducing appetite and body weight.

Erythritol

Structure	Quick Facts
	<ul style="list-style-type: none">• Naturally occurring compound in fruits and fermented foods, first discovered in 1852• In the polyol (sugar alcohol) family of sweeteners• Typically used in combination with more intense sweeteners

Erythritol is a naturally occurring sugar alcohol found in fruits, vegetables, and fermented foods. Though it was first discovered in 1852, erythritol has only been used as a non-nutritive sweetener since the 1990s. Due to its relatively low level of sweetness and high production

costs, it is typically [combined](#) with more intense sweeteners, with the addition of erythritol serving to improve mouthfeel and mask the bitter aftertastes associated with many high-intensity options. Like its cousin compound xylitol, erythritol has also been [shown](#) to have positive effects on dental health, though as a newer sweetener, it is less common in sugar-free gum products.

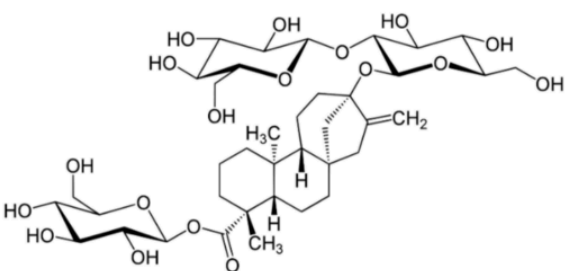
Erythritol is readily absorbed from the GI tract upon ingestion and thus does not cause the gastrointestinal distress associated with other sugar alcohols of the polyol family. In addition, the compound is naturally produced by normal metabolic processes in the human body, as discussed in a previous [newsletter](#). Still, dietary intake at concentrations typically found in sweetened beverages can cause circulating erythritol levels to increase by as much as [1000x](#) baseline values, though most is then excreted in urine without undergoing any metabolism.

As a relatively new sweetener option, erythritol has not been widely studied for its effects on body weight or glucose homeostasis. It has no effect on blood glucose or insulin in the hours following ingestion, in agreement with the default expectation for zero-calorie sweeteners. However, erythritol solutions have been shown to stimulate release of GLP-1, PYY, and CCK in acute [randomized trials](#) of lean and obese adults, and subjective feelings of hunger following an erythritol-sweetened meal reportedly exceeded those following an isocaloric sucrose-sweetened meal. Consistent with these findings, individuals who drank an erythritol-sweetened beverage were [shown](#) to consume fewer calories in a subsequent meal than individuals who drank water or beverages sweetened with sucrose or sucralose. It's important to note, however, that all of these trials involved a single exposure to the sweetener, so we cannot make any conclusions about whether erythritol would have different effects with repeated consumption.

Animal studies have found erythritol to be neutral or positive in its metabolic effects, even when control groups have not been given caloric sweeteners as alternatives. In a [study](#) of mice in early adulthood and middle age, eight weeks of erythritol supplementation increased circulating levels of the compound but did not impact body weight, fat mass, or glucose tolerance in either age group relative to controls without sweeteners. This finding persisted whether animals were otherwise fed a high-fat or low-fat diet. Another [study](#) found that dietary supplementation with erythritol-sweetened water resulted in less fat deposition in the liver than control animals given only unsweetened water, as well as slightly but significantly lower body weights and better glucose tolerance. Of note, this latter study was over twice the length of the former and did not show significant differences in body weights until after the 8-week time point, suggesting that potential benefits to energy balance are small and take an extended time to accrue to the level of significance.

In all, these animal studies and acute mechanistic investigations in humans suggest that erythritol may have neutral or modestly positive effects on metabolic health. However, in the absence of human data on longer time scales and on metrics with more direct clinical relevance, we can't yet be certain whether the apparent benefits (or lack of harm) are sustained over years of consumption.

Steviol Glycosides/Stevia Extract

Structure*	Quick Facts
	<ul style="list-style-type: none">• Natural sweeteners derived from the stevia plant native to South America• Stevioside & rebaudioside A are the most abundant steviol glycoside compounds

*This structure is stevioside, the most abundant steviol glycoside in the stevia plant.

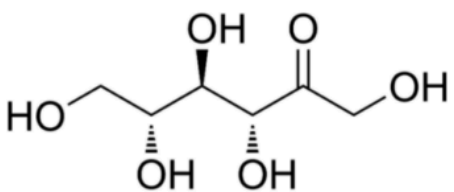
Steviol glycosides (SGs) are a group of sweet-tasting compounds derived from the South American stevia plant. Though stevia leaves have been used for millennia in food and medicine by indigenous South Americans, the first commercial stevia extract hit the market in 1970 in Japan. While crude extracts are not approved as sweeteners in the U.S., the FDA has signed off on the use of SG compounds in purified form, either in isolation or as mixtures consisting primarily of the two most abundant steviol glycosides, stevioside and rebaudioside A. Some [evidence](#) suggests that these SGs may also protect against tooth decay.

SGs are not absorbed in the small intestine but instead are metabolized by bacteria in the human colon to produce steviol, which can then be [absorbed](#) from the GI tract and enter circulation. After a subsequent metabolic step, most absorbed steviol is excreted in urine.

Steviol glycosides do not appear to result in the same weight gain and metabolic derangements apparent with some sweeteners, though this class of compounds is also likely ineffective in *improving* metabolic health. A [2019 meta-analysis](#) of RCTs on the effect of SGs on metabolic metrics reported no significant differences between the sweetener and placebo in their effects on BMI, fasting glucose, blood lipids, or HbA1c. On a mechanistic level, steviol glycosides have been shown to [stimulate](#) GLP-1 and PYY release *inex vivo* pig intestines, though effects in intact humans or animals are less clear. Though regular stevia consumption was found to alter the human gut microbiome in [Suez et al. 2022](#), it did not result in the development of glucose intolerance.

Some evidence from animal studies indicates that SGs may have net positive effects on glucose metabolism and body weight, yet it's unclear how relevant these findings are for humans. In a [study](#) of overweight female rats treated with stevia solution, water, or sucrose solution for 12 weeks, the stevia group gained significantly less weight than either the water or sucrose groups and ended the study with lower serum glucose levels. However, the doses used in this study were as high as 100x the maximum recommended daily dose for humans, which itself is quite high at 4 mg/kg body weight (or about 10 stevia packets). Therefore, it's unlikely that normal human consumption would replicate these effects.

Allulose

Structure	Quick Facts
	<ul style="list-style-type: none">• Discovered in the early 1940s• Naturally found in trace amounts in various plants• Produced synthetically for commercial use

Allulose, also known as D-psicose, is a sweet-tasting compound naturally found in trace quantities in many plants. Discovered in the 1940s, its low natural abundance means that extraction from natural sources for commercial purposes is impractical, and most allulose is synthesized chemically from glucose or fructose.

[Allulose](#) is partially absorbed from the GI tract and can enter circulation, though some is also digested into short-chain fatty acids by bacteria in the large intestine. Most ingested allulose is excreted unmetabolized through urine or feces.

Allulose has not been well studied as a sugar substitute in humans, so we have little data on its effects on body weight and glycemic control over time, or even its effects on the microbiome or brain. The information we have primarily comes from animal studies, which have [shown](#) that allulose consumption reduces total food intake, improves glucose tolerance, and causes [less weight gain](#) than other sweeteners. These positive effects have also been observed when allulose solutions were [compared](#) against solutions of pure, unsweetened water. While evidence here is limited, net benefits of allulose for metabolic health would make biological sense in light of a unique quality of this sugar substitute: it can [evidently](#) act as *substrate for SGLT1*.

Though most low-calorie sweeteners are only capable of activating T1R2/T1R3, several studies have reinforced the notion that allulose can be absorbed through SGLT1 and is thus additionally capable of activating the downstream signaling pathways dependent on this nutrient-sensing transporter. Based on what we know about the importance of SGLT1 for differentiating between real and artificial sugars and kickstarting pathways promoting satiety and food satisfaction, we would expect that allulose might therefore be more effective than other sweeteners in curbing appetite and promoting metabolic health by fooling the brain into reacting as though we've had real sugar. In agreement with this expectation, animal studies have demonstrated that allulose consumption stimulates release of [GLP-1](#) and [PYY](#) and is capable of conditioning [taste preferences](#) – a sign that it activates neural reward circuits, though activity in these brain regions in response to allulose has not been monitored directly.

What conclusions can we draw?

As long as there is a demand for low-calorie alternatives to favorite foods without compromises on taste, the number and variety of sugar substitutes will continue to increase. Those listed here do not comprise a comprehensive list, but they represent some of the most common – and controversial – sweeteners on the market today. They also illustrate many of the metabolic health considerations that apply to specific sweetener classes, as well as to sugar substitutes in general.

The preponderance of existing evidence does not support the use of sugar substitutes as a general group for controlling weight or diabetes risk in the long term. Most data indicate that they are ineffective for these purposes and may even be detrimental, particularly when added to otherwise unsweetened foods and beverages, as opposed to being used as replacements for caloric sweeteners. However, even if chronic consumption is inadvisable, short-term randomized trials show neutral or positive metabolic effects, suggesting that these compounds may be useful in a few specific, temporary contexts, such as in aiding those who are trying to wean themselves off of excessive sugar intake.

Of course, considering sweeteners as a uniform group ignores potentially key differences among the varied compounds. Most research to date on artificial sweeteners has focused on some of the oldest (yet most common) options, including saccharin, aspartame, and sucralose, and to a lesser extent, ace-K. It is therefore unsurprising that data on these specific sweeteners best align with the conclusions we've drawn above regarding sweeteners on the whole. In contrast, the metabolic effects of steviol glycosides, allulose, and the sugar alcohols xylitol and erythritol appear more positive, based on the more limited investigations of these compounds to date. Allulose in particular shows promise due to its ability to stimulate neural reward and satiation centers through activation of SGLT1, though it is also the sweetener for which we have by far the fewest results with respect to body weight and glycemic control. Still, for those who insist on swapping sucrose for a “diet” option, allulose – or other naturally occurring sweeteners on this list – might provide the best balance of low-calorie sweetness with metabolic neutrality or benefit.

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