Review

# Natural and synthetic intense sweeteners

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*Two types of intense sweeteners are available: natural sweeteners of plant origin and artificial or synthetic sweeteners. The sweeteners from natural sources with potential for commercial use include perillaldehyde, stevioside, rabaudioside, glycyrrhizin, osladin, thaumatins, and monellin. The compound miraculin, although not sweet, has the property of modifying the taste of sour food into a delightfully sweet taste. The artificial sweeteners currently in use in this country are saccharin, aspartame, and acesulfame K. In addition, sucralose, alitame, and several other sugar substitutes are in various stages of development. Although these compounds provide sweetness with minimal or no calories, some studies suggest that they may induce insulin secretion and a rise in appetite. The long-term effect of these sweeteners on weight gain and insulin secretion among various groups of the population needs to be studied.*

**Keywords:** natural sweeteners; aspartame; acesulfame K; saccharin; appetite; insulin secretion

## Introduction

Preference for sweet taste at a range of intensities is characteristic of the human species.[1,2] In the fetus, taste buds are developed by the 16th week of gestation,[3] and the newborn infant is able to respond favorably to sweetened solutions.[4]

Primitive people may have developed the desire for sweet taste as a means of survival because they considered sweetness a determinant of food safety. Berries and other plant foods which were sweet-tasting were generally found to be safe, while bitter-tasting foods were mostly toxic. Very early in the history of *Homo sapiens*, the need for sweetness could only be satisfied by consuming sweet-tasting fruits and vegetables. Progress in food technology allowed the production of refined sugar from sugar cane and beet at a relatively low price. It was then possible for the consumer to add sweetness to food to satisfy his hedonic need, and the use of sugar rose dramatically. In the United States, the consumption of sugar in the beginning of this century was estimated to be 30% of the total dietary carbohydrates, and in 1980 it surged to 54%.[5] The increase in the use of this common sweetener received a great deal of attention in the early 1960s because of its alleged adverse effects in some segments of the population. Chronic diseases such as coronary heart disease, obesity, diabetes, and hypertension were linked to excessive consumption of sugar.[6] However, a careful review and evaluation of the published results made by the Federation of American Societies for Experimental Biology did not justify the fears for sugar consumption. The study's conclusion was as follows: "Other than the contribution made to dental caries, there is no clear evidence in the available information on sucrose that demonstrates a hazard to the public when used at the levels that are now current and in the manner now practiced."[7]

Sugar is a natural sweetener that provides 4 calories per gram. It is acknowledged that excess sugar ingestion amounts to increased energy intake which, in turn, can lead to weight gain and chronic diseases associated with obesity and dental caries. Obesity is a risk factor for heart disease, cancer, diabetes, and some other diseases.[8] Therefore, there is a need for sugar substitutes, which can help reduce caloric intake, particularly in overweight individuals. Many people are aware of the possible link between sugar intake and obesity and are making an effort to control their body weight. The food industry has responded to this trend by diverting its resources into the development of alternative sweeteners. This has helped some individuals to satisfy their desire to reduce sugar and caloric intake yet enjoy sweet taste.

The most restricted item in the diets of both noninsulin-dependent and insulin-dependent diabetic individuals is refined carbohydrate.[9] Because of the acquired craving for sweetness, restricting the intake of sugar by diabetics can be difficult. Diabetic individ-

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uals have a much higher recognition threshold—up to twice as high—for sweet taste than do nondiabetic subjects.[10,11] This threshold increases the longer one has diabetes.[12] In contrast, there is no evidence for altered sweet taste sensitivity in obesity.[13] In order to increase adherence and to satisfy an individual's craving for sweetness while avoiding sugar, a safe and acceptable alternative sweetener can be useful to a person with diabetes.

Thus, diabetics or individuals who desire to lose weight are candidates for safe and effective sucrose substitutes. Several factors must be considered before determining whether a sweetener is suitable and beneficial to the general public. These include its caloric value, possible toxicity, cariogenic potential, and its effect on insulin secretion and appetite.

Attempts to provide sweetness for the diet have included modification of natural products and substitution of artificial agents. Those derived from natural products are caloric sweeteners and include fructose, sorbitol, xylitol, palatinose, and neosugar. Fructose is about 1.7 times sweeter than sucrose and is present in fruits, honey, and corn syrup. As is true for glucose, fructose does not require insulin to enter the hepatocyte or for its conversion to triose phosphates.[14]

Sorbitol and xylitol are aliphatic sugar alcohols present in fruits and vegetables. Sorbitol is only half as sweet as sucrose, and xylitol is equivalent in sweetness to fructose. The advantages of these sugar substitutes are that they are less efficiently absorbed and the blood glucose levels do not rise substantially after their use. However, they all have side-effects at high doses, and the effects of their long-term use are unknown.[14] Palatinose is chemically 6-0-α-D-glucopyranosyl-D-fructose, is a constituent of honey, and also can be formed enzymatically from sucrose.[15] It is about 42% as sweet as sucrose, is slowly absorbed, and has a low glycemic index. Palatinose is not readily metabolized by plaque bacteria and is noncariogenic.[16] The incidence of periodontosis, which frequently appears in individuals with diabetes mellitus, may be reduced by the use of palatinose in place of sugar. Neosugar is a mixture of fructooligosaccharides found in many kinds of plants (e.g., onions and asparagus root) and can also be manufactured from sucrose by using a fungal fructosyltransferase. Neosugar is not digested or absorbed by the human gastrointestinal tract to any appreciable extent and can, therefore, be considered as nonnutritive.[17] It is about 40% to 60% as sweet as sucrose.

Intensely sweet compounds can be divided into two groups: (a) naturally occurring sweeteners of plant origin; and (b) synthetic compounds. Several of these sweeteners have the potential to become commercialized as sweetening agents, which are necessary for improving the overall dietary compliance.

## Natural sweeteners

The search for sugar substitutes from natural sources has led to the discovery of several substances that possess an intensely sweet taste or taste-modifying properties. About 150 plant materials have been found to taste intensely sweet because they contain large amounts of sugars and/or polyols or other sweet constituents.[18] Although these sweeteners may have caloric value similar to carbohydrate, a very small amount is required to provide the same sweetness as sugar, and therefore, their contribution to energy intake is negligible in the amounts used. Some of these compounds that have been used or that have the potential for commercialization as sweetening agents are listed below.

*Perillaldehyde* is a constituent of the sweet volatile oil of *Perilla frutescens*. Perillartine, the α-syn-oxime of perillaldehyde, is a naturally occurring sweetener present in the oil of *P. namkemonsis* Deone[19] and is 350 times as sweet as sucrose, but has a bitter taste and low solubility in water. It is used as a sweetening agent in Japan.

*Stevioside* is a (1′-2)-linked disaccharide-containing substance present in the leaves of a small shrub *Stevia rebaudiana* Bertoni. This plant exists in Paraguay and in many eastern and southeastern Asian nations.[20] The Indians use the leaves to sweeten tea and other foods. Paraguayans use it to sweeten beverages. They also use the extract of leaves to treat hyperglycemia.[20] The pure compound can be isolated from dried leaves (6% yield) and is approximately 300 times sweeter than sucrose but exhibits a slightly bitter aftertaste. Stevioside inhibits the growth of oral microorganisms and reduces dental caries. Currently, the plant is cultivated in Japan where it is widely used as a sweetener.

*Rebaudioside A*. This ent-kaurine glycoside is the sweetest of all the *S. rebaudiana* constituents and is 30% sweeter than stevioside.[21] Compared to stevioside, this compound has a greater water solubility, has better hedonic properties, and is present in the dried leaves to the extent of 1.4% or higher.[22] This sweetener is approved for food use in Japan.

*Rubusoside* occurs in leaves of the plant *Rubus suavissimus*. This species is used in green and black tea in the southern part of the People's Republic of China and is 114 times sweeter than sucrose but has a slightly bitter taste.[22]

*Glycyrrhizin* is found in licorice root of a small shrub, *Glycyrrhiza glabra* L., grown in Europe and central Asia.[23] Glycyrrhiza is derived from Greek, which means sweet root. Licorice extracts have been used for flavoring candy, tobacco, and pharmaceutical preparations for several years. Glycyrrhizin is a saponin of glycyrrhetinic acid with an attached (1′-2)-linked disaccharide. The sweetener is present in the root as a calcium and potassium salt of glycyrrhizic acid and is isolated commercially as the ammonium salt. The concentration of the sweetener in the root may be between 7%–10% depending on the variety, source, and climatic conditions. It is 50–100 times sweeter than sucrose, has a slow onset of taste and a long aftertaste. Glycyrrhizin can act as an anticariogenic agent by interfering with the adhesion of cariogenic bacteria. Glycyrrhizin and glycyrrhetic acid both

have a chemical structure resembling a steroid. Thus, they possess mineralocorticoid and glucocorticoid properties and can influence steroid metabolism.[24] The ammonium salt of glycyrrhizin is the sweetest substance on the list of natural GRAS (Generally Recognized As Safe) food additives.

*Periandrins I-IV.* There are four oleanane-type glycosides in the roots of Brazilian licorice *Periandra dulcis* (Fabaceae). They are all 90–100 times sweeter than sucrose and have been found to produce a more rapid taste sensation than glycyrrhizin.[22]

*Cucurbitane-type derivatives:* These are glycosidic compounds from the fruits of the Chinese vine, *Thladiantha grosvenorii.* The dried fruit of this plant is known in China as "Lo Han Kuo" and is a valued folk medicine used for colds, sore throats, and minor stomach and intestinal troubles. The purified sweetener is about 250 times sweeter than sucrose.[25]

*Osladin* is a *bis*-glycoside of a new type of steroidal saponin.[26] It is 3,000 times sweeter than sucrose[20] and is present in rhizomes of the fern, *Polypodium vulgare* L. Osladin comprises only 0.03% of the dry weight of the rhizomes.

*Neohesperidin,* from citrus peel, and *naringen,* from grapefruit peel, when treated with dilute alkali and hydrogen, produce their respective intensely sweet dihydrochalcones.[27] These are 250–2,000 times sweeter than sugar; their sweet taste has a slow onset and persists for some time.[22] The sweetener is relatively inert to the action of cariogenic bacteria and is approved in Belgium for use as a sugar substitute in beverages and in chewing gum.

*Thaumatin:* The berry of an African rain forest shrub called katemfe contains two proteins, *Thaumatins I* and *II,* which have identical molecular weights. These proteins are about 100,000 times sweeter than sucrose on a molar basis and several thousand times sweeter on a weight basis.[28] There is a slow onset of sweetness that builds up to a maximum intensity, followed by a long, lingering sweet licorice-like aftertaste. These two proteins are the sweetest compounds known to humans. A process for extraction of thaumatin from the fruit is described by Higginbotham,[29] and there is increased interest for its use as a sweetener. Tate and Lyle Limited in England is marketing thaumatin under the name of Talin, and it is approved for use in the United Kingdom, Japan, and Australia. In the United States, it is given GRAS status for use as a flavoring agent in chewing gum.[22]

*Monellin:* The fruit of *Dioscoreophyllum cumminsii* (Stapf) Deils has an intensely sweet taste and is called "serendipity berry."[30] The plant is found in several regions of tropical Africa. The sweet principle is a carbohydrate-free basic protein[31,32] and is named monellin.[32] This sweetener has two polypeptide chains and has a molecular weight of about 11,000. It is 2500–3000 times sweeter than sucrose.

*Pentadin* is 500 times sweeter than sucrose and has a molecular weight of 12,000. It is isolated from fruits of the African plant, *Pentadiplandra brazzeana* Baillon.[33]

*Miraculin.* The berries of *Richardilla dulcifica,* a shrub indigenous to tropical West Africa, have long been known for their taste-changing properties. These berries, called miraculous berries or "miracle fruit," have the property of modifying the taste of sour foods such as lemon, lime, grapefruit, and rhubarb into a sweet taste after the fruit pulp has been chewed. The modifying effect lasts for up to two hours. The active principle is a glycoprotein with a molecular weight of 42,000[34] and is known as miraculin.[35] The quality of sweetness induced by this taste modifier is very similar to sucrose.

More studies in animals and humans are needed to determine the possible beneficial effects of natural intense sweeteners in diabetic and obese individuals.

## Artificial sweeteners

### *Saccharin*

The discovery of saccharin in 1879 by Constantin Fahlberg, a graduate student at Johns Hopkins University, was serendipitous. He was working on the synthesis of toluene derivatives.[36] One day during lunch, he perceived his bread to be inordinately sweet and shortly thereafter attributed it to the chemical from contact with his unwashed hands. He called the compound saccharin (*Figure 1*). Its potential as a sweetening agent in candies and bakery products was quickly recognized, and this started the non-caloric sweetener era. Saccharin is 300 times sweeter than sucrose and has a slight bitter aftertaste. It is slowly absorbed from the gut but rapidly eliminated in the urine, largely by renal tubular secretion. Saccharin does not undergo detectable metabolism in either animals or humans.[37]

Although saccharin appears to be ideally suited for diabetics and weight-conscious individuals, its safety has been repeatedly questioned since its commercial introduction in 1901. Based on a study from the Canadian Health Protection Branch which showed evidence of bladder tumors in second-generation male rats fed high doses of saccharin, the Food and Drug Administration proposed to prohibit its use in 1977.[38,39] As a result of public outcry and the need for a sugar substitute, the Congress declared a moratorium on the ban, allowing continued use until additional research on saccharin's safety could be conducted. The moratorium has been extended to 1992. However, the use of saccharin as a food additive is banned in Canada. The sweetener's long use in amounts normally consumed has not revealed any adverse health effects in humans. Several studies in humans show no association between saccharin intake and cancer. A panel of

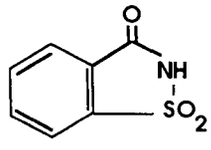


**Figure 1** Saccharin

scientists that reviewed a study by the International Research and Development Corporation concluded that "at the present level of exposure of humans to saccharin through its use as a food additive, it is unlikely to present a risk for cancer."[40] The special issue of the *Journal of Food, Chemistry and Toxicology*[40] provides an up-to-date account of the research endeavors covering various aspects of the biology, epidemiology, and toxicology of saccharin. The most recent population-based case-control investigation by Jensen et al.[41] provides further evidence that it is highly unlikely that the consumption of saccharin has contributed to the current bladder cancer risk in humans.

## Cyclamate

Cyclamate was accidentally discovered in 1937 by Audrieth and Sveda at the University of Illinois.[42] It is 30 times sweeter than sugar, slowly and only partially absorbed, and rapidly excreted into the urine unchanged.[43] Unabsorbed cyclamate is converted by intestinal bacterial flora to cyclohexylamine, a compound with sympatomimetic action.[44,45] The ability to produce this compound by bacterial enzyme systems varies greatly in the population and is increased by prolonged ingestion of the sweetener.[46] Cyclamate was introduced as a commercial sweetening agent in 1951 and is available in the form of cyclamic acid, calcium cyclamate, and sodium cyclamate (*Figure 2*). It does not have an aftertaste and overcomes the bitterness of saccharin. In 1969, evidence from the study of saccharin/cyclamate mixture implicated cyclamate and/or its metabolite cyclohexylamine[47] as a possible cancer-causing agent in rats. Cyclohexylamine has been found to give rise to testicular atrophy, reduced body weight gain, and hyperactivity.

The studies on cyclamate metabolism in rats led to the banning of this sweetener in the U.S., in 1970. In 1984, the FDA's Cancer Assessment Committee reviewed the scientific evidence and concluded that cyclamate is not carcinogenic.[48] A year later, the National Research Council came to the same conclusion noting that "the totality of the evidence from studies in animals does not indicate that cyclamate or its major metabolite, cyclohexylamine, is carcinogenic by itself."[49]

## Aspartame

Aspartame is a dipeptide, L-aspartyl-L-phenylalanine methyl ester (*Figure 3*). Its sweetness was discovered accidentally in 1965 by James M. Schlatter at G.D.

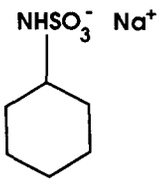


**Figure 2** Sodium Cyclamate

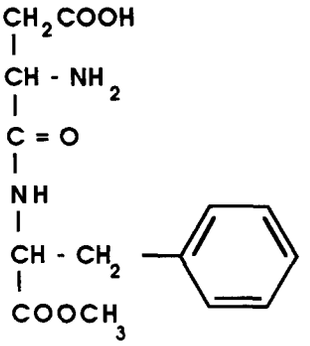


**Figure 3** Aspartame

Searle and Company.[50] Aspartame is 160–220 times sweeter than sugar and its sweet taste is almost identical to that of sucrose and with no aftertaste. Technically, it is a nutritive sweetener that provides 4 calories per gram, but compared to the sweetness of sucrose, the amount required would only supply about 0.5% of the calories provided by sugar.[51] Under certain moisture and pH conditions, as well as prolonged storage and heat, the ester bond is hydrolyzed forming the dipeptide aspartylphenylalanine and methanol. Alternatively, methanol may be eliminated by the cyclization of aspartame to form its diketopiperazine which in turn can be hydrolyzed to two amino acids, aspartate and phenylalanine (Phe).

AspartylLphenylalanine, aspartate, Phe, and the diketopiperazine product are not sweet. When aspartame is converted to these compounds in food products, a loss of sweetness is perceived.

The metabolism of aspartame has been extensively studied in mice, rats, rabbits, dogs, monkeys, and humans. The major point to emerge from the metabolism studies is that in all species tested, aspartame is broken down in the gastrointestinal tract to its constituents aspartic acid, Phe, and methanol.[52] These findings suggest that outside of the gastrointestinal tract, any toxicological activity of aspartame would result from systemic imbalances caused by increases in plasma concentration of these two amino acids and methanol.

*Aspartate.* Concern has been raised that aspartic acid from aspartame would pose a risk of causing focal brain lesion either alone or when combined with ingestion of glutamate.[53] Clinical studies by Stegink et al.[54] showed that aspartame ingestion had a relatively small effect on plasma aspartate level. Even at abuse doses of the sweetener, up to 200 mg/kg body weight, the plasma level of the amino acid remained below normal postprandial limits observed for orally fed infants and adults.[55] Aspartic acid does not cross the placenta significantly.[56] Therefore, ingestion of aspartame during pregnancy would not be expected to affect the aspartate level in fetal circulation.

*Phenylalanine.* Some investigators have voiced the fear that aspartame's Phe component may alter the level of neurotransmitters resulting in behavioral changes and possible seizures.[57,58] This possibility is based on the fact that the synthesis of some brain neu-

rotransmitters, such as serotonin, dopamine, and norepinephrine, depend on the blood supply of their precursor amino acids, tryptophan and tyrosine.[59,60] The brain uptake of these amino acids from the circulation proceeds through a carrier system common to all large neutral amino acids (LNAA), which compete to occupy the transport sites at the blood-brain barrier.[61] Thus, the transport of a given amino acid to the brain will depend not only on its absolute plasma level, but also on its concentration relative to the other LNAA.[62] This means that even when the Phe level after aspartame ingestion may be similar to that seen after a high-protein meal, the ratio of Phe to the other LNAAs will be much higher, because aspartame does not provide other LNAAs, as does a natural protein. Consumption of aspartame with carbohydrate, such as a snack accompanied by an aspartame-containing beverage, can potentiate the effect of the sweetener on the Phe/LNAA ratio because of the decrease in LNAA caused by insulin.[59] Yokogoshi et al.[63] found that plasma Phe/LNAA ratio and brain Phe are increased significantly in rats given aspartame, and this effect is enhanced when glucose and aspartame are administered together. Studies by Fernstrom et al.,[64] however, found no aspartame-induced changes in brain neurotransmitter levels at doses relevant to human exposure. It must be added that the rat experiences a larger rise in serum tyrosine than phenylalanine after aspartame gavage, and the human a larger rise in serum phenylalanine than tyrosine[65,66] which is expected to result in higher brain phenylalanine build-up in man than in the rat. Large doses of Phe ingestion by humans increase plasma Phe, tyrosine, insulin, and glucagon.[67] Insulin is known to facilitate increased uptake of the LNAAs (except tryptophan) by muscle.[59,68]

Individuals with phenylketonuria (PKU) cannot metabolize Phe normally. Unrestricted Phe in the diet of these patients can cause neuronal damage during development. These individuals must consider aspartame as an additional source of Phe. In humans, unlike aspartate, phenylalanine is concentrated on the fetal side of the placenta in a 2:1 ratio.[69] Therefore, a rise in maternal plasma Phe concentration can have twice the effect on the fetal plasma Phe concentration. However, experimental and epidemiological data on the use of sweetener during pregnancy have not shown adverse maternal or fetal effects.[69]

*Methanol.* When aspartame is hydrolyzed, approximately 10% of methanol (by weight) is released. It is oxidized by alcohol dehydrogenase to formaldehyde which is rapidly transformed to formic acid. This metabolite is responsible for ocular damage in methanol poisoning. When a single oral dose of aspartame (200 mg/kg body wt) is administered to humans, blood methanol rises to about 2.6 mg/dl which is far below the value associated with toxicity. Blood formate remains unchanged while urine formate is significantly increased, suggesting that the rate of formate synthesis does not exceed the rate of its excretion.[70,71] Not much is known about the placental transfer of methanol and its metabolites. However, the amount of methanol released as a result of ingestion of aspartame-containing beverages would be less than that present in an equal volume of fruit juice.[51]

As of October 1, 1989, the FDA has received 4,600 complaints about side-effects of aspartame, including headaches, menstrual disorders, partial blindness, upper respiratory tract symptoms, and seizures.[72] An investigation, headed by Richard Wurtman, of the Massachusetts Institute of Technology, documented about 80 people who suffered seizures following ingestion of aspartame-containing products.[73] Aspartame has also been reported to cause neuropsychiatric symptoms, such as panic attacks in a symptomless patient with mitral valve prolapse.[74] Individuals with mitral valve prolapse may have an exaggerated sensitivity to an excessive amount of aspartame.

Aspartame was approved by the FDA in 1981 for use in certain dry foods and in 1983 for carbonated beverages. Although questions continue to be raised, at this time there is no scientific evidence to dispute aspartame's safety.[75]

## Acesulfame K

Acesulfame was an accidental discovery, as were the other three artificial sweeteners described above. It emerged in 1967 from studies at Hoechst Corporation in West Germany on novel ring compounds. Acesulfame has 1,2,3-oxathiazine ring, a six-membered heterocyclic system in which oxygen, sulfur, and nitrogen atoms are adjacent to one another (*Figure 4*). It is about 200 times sweeter than sucrose but has a slight bitter aftertaste. It is soluble in water and has an extremely long storage life. Unlike aspartame, it withstands high temperatures, which makes it ideal for use in baked goods.[76] Animal experiments indicate that similar to saccharin but unlike aspartame, acesulfame reduces dental caries.[77]

Acesulfame is not metabolized by the body and is excreted by the kidneys unchanged. Due to its similarity in structure to saccharin, which has been alleged to increase the incidence of bladder cancer in male rats, its safety was a concern. However, a large number of pharmacological and toxicological studies have been conducted, and the sweetener has been found to be safe.[78] Acesulfame has been in use in the United Kingdom, West Germany, and Switzerland for some time and has been approved recently for use in the U.S.[75]

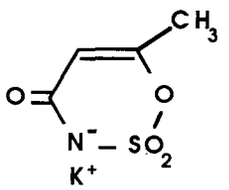


**Figure 4** Acesulfame K

## Other sweeteners

Several other artificial sweeteners are in various stages of development. Sucralose is produced by the substitution of three atoms of chlorine for three hydroxyl groups in sucrose.[79] It is about 500 times sweeter than sucrose, is non-cariogenic, and is highly stable in liquid and heat-processed foods. Thus, this product could be used in baked goods. Sucralose is poorly absorbed, but what is absorbed is excreted in the urine unmetabolized. A petition for approval of this sweetener has been submitted recently to the Food and Drug Administration by McNeil Specialty Products Company. Alitame is a new high-intensity sweetener developed by Pfizer. It is a dipeptide aspartyl alanine amide and is about 2,000 times as sweet as sucrose, 12 times sweeter than aspartame, and 6 times sweeter than saccharin at a level comparable to 10% sucrose. Alitame has no unpleasant aftertaste and is non-cariogenic. At a pH range of 6–8 and at room temperature, it is stable for more than a year. Petition for approval of Alitame has been submitted by Pfizer Inc.[80]

More recently, scientists at Nutrasweet Co. have discovered a new series of suosan-related sweeteners derived from substituted amino acids that are up to 20,000 times sweeter than sucrose.[81] The list of natural and synthetic sweeteners along with their sweetness intensity relative to sucrose is presented in *Table 1*. The exact structure of an intensely sweet compound that stimulates the taste buds is unknown. If this can be determined, more intensely sweet compounds can be synthesized and tested for their potential as "ideal" sweetening agents.

**Table 1** Natural and synthetic sweeteners

| Sweetener | Sweetness intensity Relative to sucrose |
|---|---|
| Acesulfame K | 200 |
| Alitame | 2000 |
| Aspartame | 160–220 |
| Cucurbitane (Lo Han Kuo) | 250 |
| Cyclamate | 30 |
| Fructose | 1.7 |
| Glycyrrhizin | 50–100 |
| Monellin | 2500–3000 |
| Neohesperidin dihydrocalcone | 250–2000 |
| Neosugar | 0.4–0.6 |
| Osladin | 3000 |
| Palatinose | 0.4 |
| Periandrins I-IV | 90–100 |
| Pentadin | 500 |
| Perillartine | 350 |
| Rebaudioside A | 400 |
| Rubusoside | 114 |
| Saccharin | 300 |
| Sorbitol | 0.5 |
| Stevioside | 300 |
| Sucralose | 500 |
| Sucrose | 1 |
| Suosan | 20,000 |
| Thaumatin | >3,000 |
| Xylitol | 1.7 |

## Effect of sweeteners on insulin secretion and appetite

An ideal alternate sweetener should taste like sugar, be colorless, noncariogenic, and provide minimal or no calories.[82] After ingestion, it should not affect the blood glucose or insulin levels, and it should be nontoxic.

Sensory associations with food, such as appearance, aroma, flavor, and texture, induce secretions of saliva, gastric acid, and pancreatic juice. This is known as the psychic or cephalic phase and is the initial response including insulin secretion.[83] It has a short latency and occurs before any significant increase in postabsorptive glycemia.[84] Cephalic phase of secretion has been demonstrated in man, rats, and dogs. Tordoff and Friedman[85] have shown that an increase in appetite and the resulting food intake is a function of the cephalic phase reflexes. It is believed that the sweet taste response is induced following interaction of the sweetener with a receptor protein located on the external periphery of the taste cell. Sweet taste may produce a cephalic reflex by stimulating taste receptors that can induce insulin secretion and increase appetite.[86]

Experimental evidence has indicated that consumption of saccharin and acesulfame K leads to an increased insulin secretion and appetite. In rats, oral ingestion of 0.15% saccharin (1 ml) causes rapid rise in peripheral plasma insulin level lasting up to 5 minutes without change in plasma glucose.[87] Likewise, plasma insulin level increases five minutes after injection of acesulfame K (150 mg/kg BW) in rats with no change in plasma glucose.[88] Infusion of this sweetener causes plasma insulin to increase and glucose to decrease throughout the one-hour infusion period. Additionally, acesulfame K is found to produce an increase in insulin release from isolated pancreatic islets.[89] Somatostatin normally inhibits the glucose-induced insulin release but acesulfame K antagonizes this action.[88] These findings suggest that the use of acesulfame may lead to hypoglycemia with subsequent stimulation of appetite.

In humans, simultaneous ingestion of saccharin with food causes increased intake of that food.[90] In contrast, consumption of food decreases when glucose is used in place of saccharin. Rats consuming saccharin-containing food gain more weight than those consuming unsweetened food.[91,92]

Based on a study of the effect of aspartame on appetite in human adults, Blundell and Hill[93] concluded that this sweetener increases hunger and motivation to eat and decreases the feeling of fullness. Hence, this sweetener may cause an increase in caloric intake. Other studies, however, have shown that aspartame does not affect appetite.[94] The relationship between aspartame's sweet taste and plasma insulin level is not

known. But feeding aspartame-sweetened water to rats for up to 3 weeks causes decreased plasma insulin in normal animals and increased plasma glucose in diabetics.[95,96] However, high doses of aspartame ingested by humans do not provide evidence of alterations in plasma insulin and glucose.[97,98]

Studies in humans suggest that short-term food intake increases when non-nutritive sweeteners are consumed.[99] Users of artificial sweeteners actually gain weight independent of initial body weight. Additionally, obese individuals consuming artificial sweeteners gain more weight than those near normal weight. Based on the data, differences in weight gain between artificial sweetener users and nonusers cannot be explained by an increase in food consumption. It may be the result of an elevated insulin secretion resulting in increased fat storage. There is a need to determine whether intense sweeteners possess appetite-modifying properties.

## Conclusions

The desire for sweet taste is inborn. Since the ingestion of sugar increases caloric intake and can lead to obesity, a risk factor for some chronic diseases, this common sweetener has to be restricted in the diet of diabetics. The availability of natural and artificial intense sweeteners has made it possible to offer consumers sweet taste without the calories that a diet high in sucrose implies. Since food intake is normally controlled by energy needs, the possibility exists that the use of non-caloric sweeteners may lead to increased food consumption to compensate for sugar calories. Indeed, some investigators have reported that artificial sweeteners, especially saccharin and acesulfame K, induce an increase in insulin secretion and a rise in appetite. Aspartame and saccharin were found to produce a significant increase in hunger and appetite 30–60 minutes after ingestion, while glucose produced a suppression in food consumption. There is a need for extensive research to determine the long-term effects of natural and synthetic intense sweeteners on appetite, weight gain, blood glucose, and insulin levels in normal, obese, and diabetic individuals.

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