

The Safety and Obesity-Related Effects of Artificial Sweeteners

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Abstract. Obesity is a growing global health challenge influenced by a complex combination of genetic, lifestyle and environmental factors, with high-calorie diets being one of the major contributing factors. Aspartame, sucralose, and acesulfame potassium are popular sugar alternatives for combating obesity. Although artificial sweeteners are generally considered safe by regulatory agencies, emerging research suggests that they may adversely affect metabolic health and obesity-related mechanisms. Despite their widespread use, the long-term metabolic effects of artificial sweeteners remain uncertain. This review examined the safety of common artificial sweeteners and their effects on obesity by analyzing the available evidence. According to the research, artificial sweeteners may lower calorie intake, but they may also interfere with insulin signaling pathways, change the gut microbiota's composition, and interfere with appetite management, all of which might result in weight gain and metabolic diseases. This study highlights the double-edged nature of artificial sweeteners, emphasizing their role as sugar substitutes along with their potential risks. This review provides a comprehensive reference for researchers and encourages them to further explore the long-term safety and metabolic effects of artificial sweeteners. Future research should focus on understanding the variability of individual responses to artificial sweeteners and their broader environmental and physiological impacts to guide safer dietary practices and innovative solutions to obesity.

Keywords: Obesity, safety, artificial sweeteners.

1. Introduction

Obesity has become one of the most pressing public health problems worldwide. Obesity results from genetic, lifestyle, and environmental factors, with high-calorie food and drink consumption playing a key role. Since development. The World Health Organization (WHO) reports that over 650 million persons worldwide suffer from obesity, and that since 1975, the prevalence of obesity has almost quadrupled. Obesity contributes to a range of serious health risks, including cardiovascular disease, diabetes, certain types of cancer, and reduced quality of life. Furthermore, obesity is known to be a major avoidable cause of mortality and is linked to the emergence of metabolic diseases including insulin resistance. The rising prevalence of obesity is particularly concerning because of the economic burden it places on the healthcare system, which is increasingly challenged to manage the long-term costs of treating obesity-related diseases.

Artificial sweeteners are popular for providing sweetness without added calories. Stevia, acesulfame potassium, aspartame, sucralose, and saccharin are examples of common artificial sweeteners. These compounds are commonly used in products labeled as low-calorie or sugar-free, such as soft drinks, chewing gum and desserts. They are widely used in diet products for sweetness without extra calories. However, the widespread use of artificial sweeteners has raised concerns about their long-term safety. Despite the fact that many countries' regulatory bodies deem artificial sweeteners safe, a number of recent studies indicate that they may have negative effects on metabolic health, including effects on insulin sensitivity, gut microbiota, gene expression, and appetite regulation.

This review explores common artificial sweeteners like aspartame, sucralose, and neotame. Although the U.S. Food and Drug Administration (FDA) has determined that these sweeteners are safe, certain research continues to raise doubts about their safety. In the meantime, the author summarizes the common reasons why artificial sweeteners may contribute to obesity. In view of the

controversy among the existing research findings, this paper provides a comprehensive analysis of the studies related to these several artificial sweeteners in order to provide reference for researchers.

2. The Safety of Common Artificial Sweeteners

2.1. Aspartame

Aspartyl phenylalanine methyl ester is the chemical name for aspartame, an artificial sweetener. It is a small molecule dipeptide formed by linking aspartic acid and phenylalanine through ester bond. Aspartame is a white crystalline solid, easily soluble in water, with a good sense of sweetness, and its sweetness is about 200 times that of sucrose. Aspartame is stable in the pH range of 4.3 to 6.5, but decomposes easily at high temperatures or high alkaline conditions, generating substances such as methanol, aspartic acid and phenylalanine, and is therefore not suitable for high-temperature cooking. It is a common low-calorie sweetener in meals and drinks because of its incredibly low calorific value and no impact on human energy intake due to its exceedingly low level [1].

Regulatory bodies including the European Food Safety Authority (EFSA) and the U.S. Food and Drug Administration (FDA) typically see aspartame as generally safe at ordinary consumption levels, despite the fact that phenylalanine can be hazardous to those with phenylketonuria (PKU). However, high doses or prolonged exposure may pose a risk to people with neurological disorders or lead to the long-term accumulation of methanol, which can have potentially toxic effects. For instance, some research has indicated that chronic methanol use may be linked to neurological issues, but these findings are currently being examined [1, 2].

2.2. Acesulfame Potassium

A non-caloric artificial sweetener, 6-methyl-1, 2, 3-thiazin-4(3H)-one-2, 2-dioxide potassium salt is the chemical name for Acesulfame potassium (Acesulfame-K). It is a white crystalline powder with odorless and pure sweetness, and its sweetness is about 200 times that of sucrose. Due to its great thermal and chemical stability, which allows it to resist high temperatures and a broad pH range (pH 3 to 9), the molecule is used extensively in baked products, drinks, and other processed foods. It is also soluble in water and just marginally soluble in ethanol. Acesulfame potassium itself is not involved in metabolism and is excreted directly in the urine, making it a suitable sweetener for low-calorie diets and special dietary needs.

Studies have shown that ace-K is safe for human consumption [3], and regulatory agencies such as the U.S. Food and Drug Administration and the European Food Safety Authority have confirmed this. However, the persistence of acesulfame potassium in wastewater treatment plants is an environmental concern as it is not easily broken down. It has also been shown that acesulfame potassium has some ecotoxicity and can affect aquatic organisms, but these effects are still being explored [2].

2.3. Sucralose

Sucralose, also known as 1, 6-dichloro-1, 6-dideoxy-beta-D-fructofructose-4-chloro-4-deoxy-alpha-D-glucopyranose, is a high-performance sweetener. It is made when sucrose molecules are selectively chlorinated. Sucralose, a white, powdered chemical with no flavor or smell, is about 600 times sweeter than sucrose. It may be utilized in a wide range of processed foods and beverages due to its high resilience to heat and light, stability in both acidic and alkaline conditions, and solubility in ethanol and water [4]. Sucralose has a very low calorific value and is not metabolized and absorbed by the body, making it a safe, low-calorie sweetener that is widely used in sugar-free foods, beverages, and pharmaceuticals.

The U.S. Food and Drug Administration has approved the use of sucralose in foods, and past studies have concluded that sucralose has no adverse health effects even when ingested over long periods of time. However, some recent studies suggest that sucralose may affect the gut microbiota, with potential long-term health effects that are still under investigation [5].

2.4. Neotame

Neotame is an artificial sweetener chemically known as N-(3, 3-dimethyl-2-thienyl)-L-aspartyl- α -methyl phenylalanine methyl ester. It is between 7,000 and 13,000 times sweeter than sucrose and is a mixture of phenylalanine and aspartic acid derivatives. The white, crystalline powder known as Neotame has high stability and dissolves easily in water. It doesn't break down easily and maintains its sweetness at higher temperatures and throughout a broad pH range (3 to 7) [7]. This makes Nutella widely used in low-calorie foods, beverages and bakery products. Nutella has a very low calorific value and provides almost no calories to foods, and is therefore considered an effective low-calorie sweetener for people who need to control their calorie intake.

In animal studies, neotame is expected to reduce weight gain, possibly due to its low palatability, which reduces food intake [6]. However, there are no conclusive long-term human studies that suggest any significant safety concerns. Its approval by the FDA and other regulatory agencies emphasizes its general safety at normal consumption levels.

2.5. Acesulfame K

Acesulfame K is a widely used artificial sweetener, chemically known as K hydrochloride, whose molecular structure contains an amino acid derivative and a thioester group. The structure of the molecule has a phenyl group attached to the sulfate ester, which allows Edelweiss to produce a sweet taste in the mouth without being metabolized by the body, thus making it a low-calorie sweetener. Edelweiss is a white, crystalline powder or crystal that has a strong sweet flavor and is around 200 times sweeter than sucrose. Edelweiss Sweet is appropriate for use in a range of processed foods and cookery applications due to its great chemical stability and ability to tolerate high temperatures. It is fairly stable in solution and retains its sweetness for long periods of time, while having excellent solubility and being readily soluble in water. It is typically stable in acidic to neutral settings and has a broad range of pH stability [7].

Safety studies on Edelweiss have shown a no-observed effect level (NOEL) of 667 mg/kg and an estimated general human intake of 0.05 mg/kg, which is more than 13,000 times below the safety limit. Furthermore, it has been demonstrated that Edelweiss Sweet's breakdown products are well tolerated and non-mutagenic. Its breakdown produces a minor quantity of methanol, which is eliminated by regular metabolic processes and is much below safe levels [8]. Different sweeteners affect the body in varying ways due to structural differences. While the short-term safety of these sweeteners has been corroborated by a number of studies, their potential long-term health risks remain a topic of intense scientific investigation.

2.6. Advantame

Artificial sweeteners have different chemical structures and metabolic processes, and therefore have different effects on the human body. For example, both aspartame and neotame produce phenylalanine during metabolism, but neotame is much sweeter and less likely to be consumed due to its higher potency. In contrast, sucralose and advantame are heat-stable and retain their sweetness during cooking and baking, making them more suitable for use in foods processed at high temperatures.

Although approved as safe, these sweeteners raise concerns about long-term health effects. Although a substantial amount of research supports the short-term safety of these sweeteners, there is still ongoing investigation into their long-term impacts, particularly with regard to metabolic diseases, gastrointestinal health, and the environment. In addition, the varying chemical properties of these sweeteners, such as heat stability, solubility and persistence in the environment, necessitate their further evaluation to understand their broader ecological and physiological impacts.

2.7. Summary

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3. Potential Mechanisms of Artificial Sweeteners' Effects on Obesity

3.1. Regulation of Appetite and Energy Intake

Artificial sweeteners can help alleviate obesity by reducing calorie intake, but their potential effects on appetite regulation remain controversial. According to some study, artificial sweeteners may cause anomalies in appetite management by interfering with the brain's reaction to sweetness. The brain processes sweet flavors through complex neural pathways and reward mechanisms involving the hypothalamus, striatum, and cortical regions of the brain. When artificial sweeteners are consumed, this "sweetness-calorie" association can become imbalanced [9]. It has been found that when the senses receive signals of sweetness but not enough caloric input, the appetite-driving center in the hypothalamus may be activated, prompting increased eating behavior [10].

In addition, fMRI studies show artificial sweeteners may impair sweetness reward perception, leading to higher calorie consumption later. This phenomenon may lead to dysregulation of overall energy balance by altering insulin sensitivity and psychosocial satisfaction [11].

3.2. Insulin Sensitivity

Insulin is a central hormone in maintaining stable blood glucose levels, and its action is dependent on the sensitivity of target tissues to insulin. Chronic intake of artificial sweeteners may negatively affect insulin sensitivity [12]. Animal experiments have shown that aspartame can alter insulin signaling pathways, for example, by reducing the level of insulin receptor substrate (IRS) phosphorylation in liver and muscle tissues, impairing the efficiency of insulin action [13]. In addition, another study noted that artificial sweeteners promote abnormal insulin secretion by activating the sugar-sensitive receptor T1R2/T1R3 complex in the small intestine, which may further disrupt glucose metabolism. Over time, this aberrant insulin production may result in insulin resistance, which impacts metabolic health and body weight [14].

3.3. Effects of Gut Flora

Artificial sweeteners can significantly affect metabolic health by changing the makeup of gut flora, which is a crucial component in the control of metabolism. Studies have shown that artificial sweeteners such as sucralose may reduce the number of probiotic bacteria (e.g., *Bifidobacterium* and *Lactobacillus*) while increasing the proportion of potentially pathogenic bacteria (e.g., *Bacteroidetes* spp. and *Clostridium* spp.) [15]. In addition, artificial sweeteners may modulate obesity risk by affecting gut barrier function, metabolism of short-chain fatty acids (SCFAs), and inflammatory pathways. Research suggests that changes in gut flora may weaken the inhibitory effects of gut cells on inflammation by reducing the production of SCFAs such as butyric and propionic acids, which in turn increases systemic inflammation levels. This inflammation may lead to weight gain and insulin resistance. Artificial sweetener consumption has been linked to a decrease in the variety of gut flora in human individuals [16].

The causal role of gut flora in metabolic regulation is directly supported by a study that demonstrated, through a fecal flora transplantation assay, that mice that received transplants of saccharin-treated flora showed decreased insulin sensitivity and weight gain [17].

3.4. Gene Expression and Metabolic Pathways

Artificial sweeteners may affect key physiological processes such as fat and glucose metabolism by modulating gene expression and metabolic pathways. They have been found to act on specific signaling pathways, such as the peroxisome proliferator-activated receptor (PPAR) pathway and the insulin pathway, which in turn affect metabolic health.

3.4.1. PPAR

The three isoforms of PPAR—PPAR α , PPAR β/δ , and PPAR γ —are crucial transcription factors that control lipid metabolism. Artificial sweeteners may promote adipocyte differentiation and lipid storage by up-regulating the expression of the PPAR γ gene, which can lead to weight gain. For example, studies have shown that aspartame may activate signaling molecules upstream of PPAR γ , such as phosphatidylinositol-3-kinase (PI3K) and AKT pathways. These alterations increase the expression of fatty acid binding protein (FABP4) and key enzymes for adipogenesis (e.g., fatty acid synthase FASN) in adipocytes, promoting fat storage [18].

3.4.2. Insulin Signal

Artificial sweeteners may also alter glucose metabolism by affecting key genes in the insulin pathway. Members of the IRS family are central nodes in insulin signaling, particularly IRS-1 and IRS-2. Experiments have shown that chronic intake of saccharin reduces the expression level of the IRS-1 gene and decreases its phosphorylation, a change that impairs the efficiency of insulin action in the liver and muscle, leading to insulin resistance. In addition, artificial sweeteners may further exacerbate abnormalities in glucose regulation by down-regulating the gene expression of glucose transporter protein (GLUT4), which reduces glucose uptake by muscle tissue [19].

3.4.3. Fatty Acid Metabolism

Artificial sweeteners may affect energy expenditure in terms of fatty acid metabolism by changing the expression of genes associated with fatty acid oxidation (e.g., CPT1A and carnitine palmitoyltransferase 1A). Reduced expression of these genes decreases the ability of mitochondria to oxidize long-chain fatty acids, leading to lipid accumulation and thus weight gain [20].

3.4.4. Glucagon-like peptide-1 (GLP-1)

It has been found that artificial sweeteners may also inhibit the GLP-1 signaling pathway, a peptide hormone secreted by the gut that enhances insulin secretion and inhibits glucagon release through activation of adenylate cyclase (AC) and cAMP signaling. Artificial sweeteners may reduce the expression of the GLP-1 gene, weakening this regulatory mechanism and thus adversely affecting metabolic homeostasis.

4. Conclusion

The utilization of artificial sweeteners has demonstrated a consistent upward trajectory in recent years. In terms of safety, although the majority of studies have concluded that artificial sweeteners are safe when consumed at routine levels, the metabolites of some sweeteners (aspartame) may pose a potential risk to specific populations or under high-dose conditions. In regard to the impact of artificial sweeteners on obesity, research has indicated that these substances may influence metabolic health through a range of mechanisms. However, the precise role of these mechanisms remains a matter of contention and is shaped by individual differences and the heterogeneity of research methodologies. When considered collectively, the evidence suggests that, while effective sugar substitutes, artificial sweeteners shouldn't be the primary solution for obesity.

To provide individual dietary choices a stronger scientific basis, future studies should focus on the long-term consequences of artificial sweeteners on safety and metabolic disorders. Nutrition researchers are expected to contribute further.

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