A Narrative Review of Artificial Sweeteners

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Abstract: Nonnutritive sweeteners (NNS) are a class of food additives used by the food industry worldwide to combat diseases such as weight gain and type 2 diabetes by maintaining their sweet taste while maintaining low or no calorie intake. Artificial sweeteners have been widely used in food-production industry for their advantages of supernal sweetness, no nutrition and low calorie. However, the safety and effectiveness of artificial sweeteners remain controversial. This paper introduces the metabolic characteristics and detection methods of five common artificial sweeteners, including Acesulfame-K, aspartame, neotame, saccharin and sucralose. Suggestions on the development of artificial sweeteners were put forward to provide reference for further rational development and safe use of artificial sweeteners.

1 INTRODUCTION

More than a century has passed since saccharin, the oldest NNS (Mooradian, 2013) was first used. American children are reported to be consuming NNS every day, up from 30 percent in 2008. Public interest in NNS has increased because they lessen the energy density of the diet without loss of sweetness. A variety of artificial sweeteners have been discovered and applied in different fields, especially in the production of beverages and foods, such as baked goods, dairy products and beverages (Dunford, 2018)

By definition, NNS, also known as very low-calorie sweeteners, artificial sweeteners, no-calorie sweeteners and high-intensity sweeteners, are sweeter than nutritional sweeteners like table sugar. As a result, small amounts of NNS are needed to create the sweetness needed by many nutritional sweeteners. In this way, they do not offer or offer low-calorie ones (Gardner, 2012).

The effects of NNS on human metabolic responses are complex. Some studies have shown positive effects, such as significant weight loss in the short term and weight control in the long term (Li, 1997). Some have no effect on glycemic control in patients with type 2 diabetes (Grotz, 2003). Some studies have shown many adverse effects, including cardiovascular, renal toxicity, obesity, and cognitive effects (Lohner, 2017). There are some physiological mechanisms for the occurrence of these symptoms, such as intestinal microbes causing intestinal inflammation and so on, thus promoting the occurrence of these symptoms

A number of metabolic disorders associated with obesity. This review aims to explain how artificial sugars produce sweetness, introduce different types of artificial sugars, their effects on human health, and explore possible future research areas from articles collected on Pubmed.

2 THE PRINCIPLE OF ARTIFICIAL SWEETENERS CREATE THE TASTE OF SWEETNESS

These two G protein-coupled receptors of the c family can detect all sweet compounds (GPCR) T1R2 and T1R3 expressed on the surface of mammalian taste buds (Li, 2002). Studies have shown that Sac is a single master site in mice that affects the response to several sweet substances, including preference for sucrose, acesulmae-K and dulcin (Fuller, 1974). Sweet transduction of natural sweeteners may be explained by the activation of adenylate cyclase, adenosine 3', 5' -cyclic adenosine phosphate (cAMP) dependent membrane generation (Streem, 1991), K+ channel inactivation (Avenet, 1998), and Ca2+

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(Lindemann, 1996) depolarization after flavor transducers bind to receptors. The opening of voltage-gated Na+ and K+ channels leads to action potentials in presynaptic neurons (Cummings, 1993).

Some studies have shown that artificial sweeteners increase sweetness intensity by increasing affinity for one or more sites on T1R2 and T1R3 receptors (Xu, 2004). Some studies have shown that receptors T1R2 and T1R3 respond differently to artificial sweeteners. Daly et al demonstrated that the commonly used NNS sucralose, saccharin and acesulfame K activated T1R2 and T1R3 in pigs, while NNS aspartame and cyclohexylsulfamate did not (Daly, 2001).

3 TYPES OF ARTIFICIAL SWEETENERS

The five NNS approved by the FDA include Acesulfames, aspartame, neotame, saccharin, and sucralose (Brown, 2010). In addition, basic information about these five non-nutritional sweeteners is shown in Table 1.

Saccharin is the oldest artificial sweetener used. It was developed by Johns Hopkins University in 1878. The FDA approved it in 1879. It is 200 to 700 times sweeter than sucrose (Bermann, 2017).

Aspartame was first discovered in 1965. It consists of two amino acids, phenylalanine and aspartic acid, with methanol as the main chain. It was approved by FDA in 1981. It is 200 times sweeter than table sugar. Aspartame's safety remains in question as its metabolism ultimately leads to the formation of formaldehyde, formic acid and diketopiperazine.

Acesmeline K was first discovered in 1967 and approved for use by the FDA in 2003. It is 120 times sweeter than sucrose (Rymon, 1991). Because it is thermally stable and has a bitter aftertaste when used alone, it is used in cooking and baking. When used in cooking and baking, it is often mixed with other sweeteners, such as sucralose or aspartame (Horne J, 2002).

Neotame was approved by the FDA in 2002 and is currently the most effective sweetener available. It is chemically related to aspartame. It is 7000 times sweeter than sucrose (Prakash I, 2007).

Sucralose was synthesized in 1976 by replacing chlorine with three hydroxyl groups in sucrose and was approved by the FDA in 1999. It is 600 times sweeter than sucrose (Arora, 2009).

Table 1: The basic information of five Nonnutritive Sweeteners.

Sweetener	Chemical formula	*Sweetness	FDA-approved date
Saccharin	$C_7H_5NO_3S$	200 - 700	1879
Aspartame	$C_{14}H_{18}N_2O_5$	200	1981
Acesulfame-K	$C_4H_4KNO_4S$	120	2003
Neotame	$C_{20}H_{30}N_2O_5$	7000	2002
Sucralose	$C_{12}H_{22}O_{11}$	600	1999

*Sucrose=1 (Relative to a 10% sucrose solution) Different numbers indicate effect in different foods

4 ARTIFICIAL SWEETENERS AND HUMAN HEALTH

4.1 Artificial Sweeteners and Obesity

Feijo et al., Foletto et al., and rats showed that intake of saccharin or aspartame promotes weight gain without significant changes in caloric intake, insulin resistance, and fasting leptin (Feijo, 2013). A large number of studies have shown that the use of NNS is positively correlated with weight gain (Stellman, 1986). In a cohort study completed by Chia et al., NSS users significantly increased BMI and waist circumference from 1984 to 2012 with a median follow-up of 10 years of 1,454 participants (741 males, 713 females) (Liu, 1990). A cohort study included 3,033 volunteers whose mothers consumed artificially sweetened and sugary drinks between 2009 and 2012. Studies have shown an association between daily intake of NNS and a two-fold increased risk of being overweight at age 1

4.2 Effects on Gut Microbes

The effects of NNS on microbes vary. Table 2 shows the effects of five non-nutritive sweeteners on the gut microbiome.

Due to the fast absorption and excretion rate of acesulphine potassium into systemic circulation, it has little effect on colon flora (Magnuson, 2016). Similarly, aspartame has little effect on colonic flora (Stegink, 1987) because it is rapidly absorbed in the duodenum and jejunum. On the other hand, a small amount of saccharin (less than 15%) is not absorbed as a whole molecule and thus enters the colon, affecting the microflora (Plaza-Diaz, 2020). In in vitro model studies, saccharin increased the number of bifidobacterium (Renwick, 1985). The minimum amount of sucralose (less than 15%) is absorbed and hardly metabolized. Thus, more than 85% of sucralose reaches the colon. However, more than 94% were recovered from feces, and no structural changes occurred, indicating no impact on microbial community (Magnuson, 2016). The effect of neotsuan on gut microbes has not been assessed, as only trace amounts of neotsuan are needed to sweeten foods. It can be metabolized quickly. Therefore, neotame is unlikely to affect gut microbes.

Table 2: The effect on microbiome in the gut of Five Nonnutritive Sweeteners.

Sweetener	Effect on microbiome in the gut
Saccharin	Affect bacteria such as Bifidobacterium
Aspartame	Almost no effect since large amount is absorbed
Acesulfame-K	Almost no effect since large amount is absorbed
Neotame	-
Sucralose	Almost no effect

4.3 Influence on Kidney

Recent studies have also found a relationship between NNS intake and chronic kidney disease (including proteinuria, the threshold of the albumin/creatinine ratio >17mg /g in men and >25mg /g in women) and decreased renal function. In a cross-sectional analysis of 9358 subjects from 1999 to 2004, soda consumption and NNS may be associated with proteinuria. In addition, a study of 3,318 women from 1989 to 2000 found that drinking more than two servings of artificially sweetened soda a day tripled a woman's risk of kidney function decline.

5 CONCLUSION

This literature review combines systematic reviews, prospective cohort studies, and meta-analyses to illustrate the possible mechanisms of neural network sweetness and the possible negative effects of neural network on human body. Although NNS created as an alternative to sugar attempts to provide the same sweet intensity as the nutritional sweetener sucrose, there is substantial evidence of profound negative effects on the human body, including host microbes, weight gain, and kidney health. Although NNS are thought to be healthier than sugar, most data contradict this claim.

Future research should include novel sweeteners such as naturally occurring rare sugars, including D-Allulose (D-Psicose), D-Tagatose, D-sorbide and D-Allose, their effects on humans, and the feasibility of using them in mass production.

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