Progress in Nutrition 2018; Vol. 20, Supplement 2: 36-43 DOI: 10.23751/pn.v20i2-S.5901

A review of the health hazards of artificial sweeteners: are they safe?

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Summary. The increasing prevalence of obesity and diabetes mellitus has led to an increased production and consumption of artificially sweetened foods all over the world. Artificial sweeteners are high-intensity sweeteners which contribute no calorie. As a result, most of these foods may be sold with a "healthy" or "diet" labeling; however, there have been lots of controversy regarding their safety and adverse health effects. Therefore, the present article review aimed to summarize the results of most relevant studies concerning side effects of artificial sweeteners. Accordingly, a search of several databases was performed to identify all related manuscripts from 1980 to 2016. As a result, most of the available animal studies demonstrated that chronic exposure to artificial sweeteners led to increased body weight, impairment of glucose and insulin homeostasis, alteration in gut microbiota, neurobehavioral effects and also induction of kidney injury and cancer. However, the existing clinical and epidemiologic data are partly inconsistent to make a definitive conclusion regarding some of those adverse effects. In conclusion, consumers should be aware of the potential side effects of artificial sweeteners and it may be recommended that only minimal amounts of NNS could be consumed.

Keywords: artificial sweeteners, non-nutritive sweeteners, side effect, adverse effect, obesity, metabolic, nephrotoxic, gut microbiome

Introduction

Artificial sweeteners are a class of food additives that provide sweet taste without increasing caloric intake. They are also named as non-nutritive sweeteners (NNS), high-intensity sweeteners, and low caloric sweeteners (LCS) (1-3). The increasing prevalence of obesity and diabetes mellitus has led to an increased production and consumption of artificially sweetened foods including cereals, biscuits, jams, candies, chewing gums, ice creams and different kinds of beverages over the world (2,4-5).

There are six LCS approved by the US Food and Drug Administration (FDA) to be consumed by general public, including aspartame, acesulfame- potassium (acesulfame-K), advantame, neotame, saccharin, and sucralose. Sugar alcohols like sorbitol are low intensity sweeteners with sweetness near to sucrose, so they are not included in NNS category (1,5-6).

The FDA and other advisory agencies have set an acceptable daily intake (ADI) for each non-nutritive sweetener. ADIs are the maximal amount of NNS considered to be safe for human consumption (7). The most popular non-nutritive sweeteners are sucralose, aspartame and acesulfame-K (5,8), which will be briefly described below.

Sucralose

Sucralose (Splenda) is a synthetic tri-chlorinated disaccharide which was discovered in 1976 and approved by FDA in 1998. Sucralose is 450–650 times sweeter than sucrose (9-10). It is used in wide variety of products over the world because of its intense sweetness and other physicochemical properties like

high solubility in water and stability over a wide range of pH and temperature (10-13). The ADI for sucralose is 5mg/kg bw/day in the United States (FDA) and 15 mg/kg/d in the European Union as recommended by Scientific Committee on Food of the European Commission (SCF) (9). Most of the ingested sucralose (65-95%) is excreted relatively unchanged in feces and just negligible amounts can be absorbed; therefore, it provides no calories (14).

Aspartame

Aspartame (L- aspartyl- L-phenylalanine methyl ester; ASP) was discovered in 1965 and got its initial approval from FDA in 1974. Aspartame was approved as a general purpose sweetener by FDA in 2006. It is a white, odorless powder, approximately 200 times sweeter than sucrose (15-17). Aspartame is unstable during prolonged heating; therefore, it cannot be used for cooking. It also decomposes in liquids during storage (17-18). The ADI of aspartame is 50 and 40 mg/kg bw/day, respectively based on the United States (FDA) and European Union (JECFA[1]) recommendations (7,19).

Once ingested, aspartame is metabolized to aspartic acid, phenylalanine and methanol in the ratio of 50:40:10 %, respectively. In the liver, methanol is oxidized to formaldehyde which is accompanied by the formation of superoxide anion and hydrogen peroxide (2,19-20). Therefore, aspartame intake can increase the production of pro-oxidants in body and cause adverse health effects (21-23); especially in some conditions like diabetes, aging and intensive physical activity which there are innately increased production of free radicals.

Acesulfame-potassium

Acesulfame-K is an acidic cyclic sulphonamide derivative. It was discovered in 1967 and approved by FDA in 1998. Acesulfame-K is 200 times sweeter than sucrose and has high water solubility and heat stability, so it can be used in cooking and baking (2,24). Acesulfame-K may cause a bitter taste when used alone; therefore, it is mostly used in combination with other sweeteners to mask this taste (17,24-25). It is not metabolized in the body; thus it provides no calories. ADI for acesulfame-K is set as 15 mg/kg of body weight/day based on the FDA and JECFA recommendations (24).

Artificial sweeteners were commercially produced to substitute for sugar in order to decrease the increasing burden of metabolic diseases, while giving the same pleasure of eating sugar sweetened products. Most of these foods may be sold with a "healthy" or "diet" labeling; however, there has been lots of controversy regarding their safety and adverse health effects. Therefore, the present article review aimed to summarize the results of the relevant studies concerning adverse health effects of artificial sweeteners.

The side effects that have been more taken into account in experimental and epidemiological studies are: obesity and metabolic syndrome, alteration in gut microbiota, cancer and the hepatotoxic, nephrotoxic and neurobehavioral effects. Each of these five issues is addressed in detail in this review.

Adverse health effects of artificial sweeteners:

Obesity and metabolic syndrome

Some of the epidemiological (26-35) and experimental studies (36-42) revealed that long-term consumption of NNS-containing products was associated with an increased risk of developing overweight, obesity, metabolic syndrome and type 2 diabetes. A recent article review including some relevant prospective cohort studies indicated that the consumption of artificially sweetened beverages might increase weight gain and risk of metabolic syndrome, type 2 diabetes, hypertension and cardiovascular disease (26). Results of a large epidemiological study using data from the Third National Health and Nutrition Examination Survey (NHANES III) revealed that aspartame intake was associated with greater glucose intolerance in obese individuals (35).

Furthermore, results of a recent prospective study by O'Connor et al. (43) showed that consuming artificially sweetened beverages instead of sugar sweetened beverages did not reduce total energy intake and incidence of adiposity in UK-resident adults.

Moreover, oral administration of aspartame to albino rats, resulted in hyperglycemia and hyperlipidemia (44-45). Collison et al. (39-40) demonstrated that long

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term exposure of mice to aspartame (55 mg/kg of body weight/day) from neonate to the end of the fifth month, increased body weight, visceral fat and fasting glucose levels and decreased insulin sensitivity in adulthood. It was reported that chronic exposure (40 weeks) of mice to acesulfame-K led to hyperlipidemia and hyperinsulinemia without any change in insulin sensitivity (46) and that it might enhance the preference for sweet foods intake in adulthood (47). There are also evidences that high sucralose intake alters glucose, insulin and glucagon-like peptide-1 levels (9,48-80).

Overall, chronic consumption of artificial sweeteners may be associated with an increased risk of weight gain and other metabolic dysfunctions such as hyperglycemia and hyperlipidemia through some default mechanisms including: increasing the intestinal absorption of glucose by activation of sweet taste receptors (T1Rs)[2] in the intestine (36,47, 51-52), a compensatory energy intake by decreasing the ability to anticipate the content of foods (53), increasing insulin secretion and adiposity (54) and alteration in gut microbiota (8,41,55).

Gut microbiota dysbiosis

Several clinical evidences demonstrated that the disruption of gut microbiota was associated with numerous diseases including obesity, metabolic syndrome, type 2 diabetes and some inflammatory diseases (8, 56-57).

It was also revealed that long term consumption of artificial sweeteners disrupted the balance and diversity of gut microbiome in both mice and humans by decreasing the number of beneficial bacteria like lactobacilli and bifido bacteria (8,41,55). For example, significant dysbiosis of gut microbiome was reported after feeding rats with saccharin (58), sucralose (9,55), aspartame (56-62) and acesulfame k (62). Of interest, Abou-Donia et al. (55) showed that the sucralose- induced dysbiosis in rats was not fully reversible even 3 months after cessation of sucralose. Therefore, their consumption might affect metabolic health in susceptible individuals.

Mechanisms by which artificial sweeteners may affect gut microbiome have not clearly been understood but may be related to their metabolites. Aspartame metabolism yields methanol and small amounts (~1.5%) of aspartyl phenylalanine diketopiperazine (DKP), which both seem to have antimicrobial properties and may affect the gut microbiota (60-61). It was also suggested that sucralose might be metabolized to 1,6-dichloro-1,6-dideoxyfructose (1,6-DCF) or other aldehydes in vertebrate intestine (9,55). These metabolites can adversely affect different biological processes in bacterial and mammalian cells (63).

Moreover, it seems that the NNS consumption maybe affect the gut microflora of some individuals more than others, possibly due to individual differences in genetic, microbiome composition, dietary habits, medications and etc (8).

Hepatotoxic and nephrotoxic effects

Consumption of non-nutritive sweeteners, especially aspartame has been linked to liver and kidney dysfunction according to some experimental studies (64-69). Bahr and Zaki showed that aspartame intake significantly increased blood urea nitrogen (BUN), serum creatinine and potassium levels in male rats (20). Similar findings were also reported by Waggas et al. (69) in aspartame fed female rats, along with significant structural changes in their renal tubules compared to control group.

It was also shown that the administration of aspartame altered the antioxidant defense system in the liver and kidney of rats (20, 66-70). However, to the best of our knowledge such adverse effects by aspartame intake have not been assessed in humans. Oxidative stress is characterized by increased levels of prooxidants like reactive oxygen species (ROS) and reactive nitrogen species (RNS) and/or decreased the antioxidants level that could lead to cell dysfunction and degradation (71).

It was revealed that decreased activity of antioxidant enzymes in aspartame fed animals might be due to methanol production which is then converted to formaldehyde. This process is accompanied by the elevation of nicotinamide adenine dinucleotide (NADH) level and formation of superoxide anion which may be involved in lipid peroxidation and impairment of antioxidant status (72-74).

2 1- Taste 1 receptors

Cancer

The genotoxic and carcinogenic effects of non-nutritive sweeteners have been very controversial among researchers. Study on their carcinogenic effect has started since 1970, when the FDA banned cyclamate due to increased incidence of bladder tumors in rodents (75). It was also reported that high doses of artificial sweeteners like saccharin and sucralose led to carcinoma and mutagenesis in rats (24,76-77).

Results of Soffritti et al. (78) and Belpoggi et al. (79) showed that the administration of aspartame (4–100 mg/kg of body weight/day) induced carcinogenic lesions in multiple tissues including peripheral nerves, renal pelvis, ureter and lymphatic organs of rats. Furthermore, Rencuzogullari et al. (80) and Alsuhaibani (81) reported significant dose dependent chromosomal aberrations in aspartame treated human lymphocytes and mice bone marrow cells, respectively. However, other animal studies did not support the carcinogenic effect of aspartame (75, 82-83).

In an article review by Marinovich et al. (7) results of the most relevant epidemiological studies concerning carcinogenic effect of artificial sweeteners (mainly aspartame) were assessed. It was concluded that there was no significant association between aspartame intake and different cancers' risk. Whereas, a most recent systematic review consisting of five large epidemiological studies demonstrated a significant direct association between artificial sweetener consumption and laryngeal cancers, urinary tract tumors, non-Hodgkin lymphoma, multiple myeloma and leukemia (84).

Overall, long term use of artificial sweeteners may induce carcinogenic effect through some mechanisms like, increasing oxidative stress and nucleic acid oxidation (20). Reactive oxygen species (ROS) have an important role in the development of genomic instability. Abhilash et al (68). reported that a small amount of aspartame significantly increased the plasma methanol level that was accompanied by increased production of free radicals and induction of DNA damage and chromosomal aberrations. Furthermore, Alleva et al. (85) demonstrated that aspartame was a potential angiogenic component that could stimulate induction of cytokines, growth factors, and vascular endothelial growth factor by increasing ROS production.

Neurobehavioral effects

Based on the existing evidences, one of the possible side effects of artificial sweeteners is neurological and behavioral disturbances (86-96). It was reported that aspartame fed rats showed some signs of neurotoxicity and hypersensitivity reactions (86-90). Recently, Collison et al. (40) demonstrated that aspartame-fed mice had impaired learning abilities compared to control group and interestingly, male offsprings were more vulnerable to this adverse effect than females. Neurobehavioral adverse effects like decreasing memory and cognitive functions were also reported following chronic exposure of mice to acesulfame-K (91).

In regard to clinical data, results of a recent study by Lindseth et al. (96) showed that the intake of aspartame at half dose of the ADI may cause irritable moods, depression and lower performance in healthy adults. Moreover, some of the previous clinical trials demonstrated better spatial memory, word recall and reaction times in subjects consuming sugar sweetened versus artificially sweetened beverages (93-94). However, those adverse effects were not reported in some other clinical trials (97-98).

Although the mechanisms of neurotoxic effects of artificial sweeteners have not clearly stated, these may be due to the glycolysis inhibition and adenosine triphosphate (ATP) depletion in the hippocampus and/or alterations of brain neurotransmitters by imbalance of precursor amino acids (phenylalanine and aspartic acid) in brain level (91, 99-100). Phenylalanine and aspartic acid are main metabolites of aspartame and are naturally found in foods. They easily cross the blood-brain barrier and act as precursors of neurotransmitters. There is a controversy about the increasing plasma levels of these amino acids following aspartame intake. However, high plasma concentration of these amino acids can be neurotoxic when unaccompanied by the other amino acids.

Discussion and conclusions

Nowadays, artificial sweeteners have been most popular especially among overweight, obese and diabetic patients and adolescences. Most of the people consider the artificial sweetened products as "healthy diets" due to the reduction of energy density of diet; however,

at present there has been lots of controversy regarding their safety and adverse health effects.

Most of the available animal studies demonstrated that chronic exposure to artificial sweeteners, in particular aspartame, led to an increase in body weight, impairment of glucose and insulin homeostasis, neurobehavioral alterations and also induction of kidney injury. Moreover, it was mentioned that exposure to artificial sweeteners at critical periods of development like prenatal stage might increase the incidence of these adverse effects in adulthood.

However, the existing clinical and epidemiologic data are partly inconsistent to make definitive conclusion regarding the health hazards of artificial sweeteners. One main reason for this controversy is using various assessment procedures for each side effect alongside different statistical analytical methods and considering or not considering the demographic and clinical confounding factors. Secondly, the individual intake of NNS may not be assessed thoroughly, because some people may not be aware of food ingredients and mostly there is a blend of different NNS in a food product. Thirdly, it should be considered that most of the prospective cohort studies evaluated the NNS intake of healthy adults and its effect on incidence of disease while, NNS consumption of overweight, obese and diabetic patients seems to be higher than that of healthy adults.

In conclusion, consumers should be aware of the potential side effects of artificial sweeteners, albeit there are not conclusive clinical data about those adverse effects. Thus, at present, it may be recommended that only minimal amounts of NNS be consumed.

Acknowledgments

This study was supported by Kidney Research Center, Tabriz University of Medical Sciences (Tabriz, Iran). The authors have declared that there is no conflict of interest.

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