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EC NUTRITION
Review Article

Saccharin by Nutritional Metabolism Perspective

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Received: January 29, 2020; **Published:** February 19, 2020

Abstract

Saccharin is one of the first artificial sweeteners produced. It was found "accidentally" by Constantin Fahlberg and Ira Remsen at the end of a laboratory day. It is a benzoic sulfonate type compound and has 300 times sweeter taste than sucrose. It gives a bitter and metallic taste afterwards. It is very slightly soluble in water, but Na salt dissolves very well. It is not metabolized in the body, so it is quickly excreted in the body with urine. Because the pH in the urinary system of rats is higher than 6.5, consumption of 5% and above saccharin by diet may cause bladder cancer in male rats. It is called "reasonably anticipated to be a human carcinogen" for humans. According to the final evaluations, NOAEL value was determined as 500 mg/kg BW and ADI value was determined as 5 mg/kg BW for Na-saccharin. It can disrupt food consumption, glucose absorption and insulin secretion, and cause glucose intolerance. Increased body fat tissue can lead to hyperinsulinemia and insulin resistance.

Keywords: *Saccharin; Artificial Sweeteners; Sucrose*

Introduction

Saccharin is the first non-nutrient sweetener produced. Although it is also available as saccharin acid, it is generally sold in the market as sodium (Na), potassium (K), calcium (Ca) salt. It dissolves very little in water, but the Na salt dissolves well. It remains stable under normal use and storage conditions [1]. It is not metabolized in the body. When administered 500 mg/kg/day as a level (NOAEL) that Do not show negative effects in male rats, there were contradictions regarding its safety due to the bladder tumor. However, when calculating the acceptable daily intake level (ADI) for people, EFSA used 200 coats instead of 100 as the safety factor and reported the ADI value temporarily as 2.5 mg/kg/day [2].

Saccharin $C_7H_5NO_3S$ has a molecular structure and has a 300 times sweeter taste than table sugar [1]. However, the unpleasant bitter and metallic taste that is heard afterward and even sweet taste can be perceived even in 1: 100000 resolution [3]. Constantin in the historical process It was found by chance by Fahlberg and Ira Remsen when working with coal tar. While she was eating after her lab work, she noticed the unusual sweet taste in her hand, napkin and cup, and when she returned to the lab, she discovered that the source of this taste was o-sulfobenzoic acid, which reacted with phosphorus (P), chlorite and ammonia. As a result of the reaction, benzoic sulfimide was formed and he called this compound saccharin [4]. Its production has been kept under strict control and it has been provided only through pharmacies. Its use increased during the First World War and its production continued until the Second World War. In the Second World War, its use increased again due to the scarcity of sugar and calcium salt was produced as a soluble alternative in the early 1950s [5].

Industrial production increased rapidly after its discovery. There are two different production methods. The most used method is the original Remsen-Fahlberg production. With this method, toluene is treated with chlorosulfonic acid and ortho- and para-toluenesulfonyl

chloride is produced. By reacting with ammonia, ortho- and para-toluene sulfonamide are formed. Ortho-toluene sulfonamide is oxidized and saccharin is formed after heating. The other method is the methyl anthranilate or anthranilic acid starting agent, which is naturally found in grapes, and it reacts with sodium nitrate, sulfur dioxide and chlorine, and 2-chlorosulfonylbenzoic acid methyl ester is formed. After being treated with ammonia, it is transformed into amide form and saccharin production is realized. Since saccharin is not soluble well in water alone, it is converted into sodium and calcium salts [3-5].

Metabolic pathway in organism

Saccharin can be present in ionized (saccharin anion) and non-ionized form depending on the pH of the medium. The non-ionized form can be rapidly absorbed from the stomach of the species with low pH stomach, while it can be absorbed slowly from the stomach of the species with high pH or from the small intestine. In humans and rats, saccharin is absorbed at a rate close to 100% but slowly and is rapidly excreted in the urine [6]. 99% of the saccharin taken in the first 24 hours accumulates in the urine in 96 hours. The remaining 1% remains in the bile. Since biotransformation was not metabolized and not metabolized, there is no evidence that it creates metabolites in the body. For this reason, urine excretion can be considered as a measure of digestive system absorption and faeces excretion can be considered as a marker of unabsorbed saccharin [4,6]. However, when the dietary intake above 5% (NOAEL value 1%: 500 mg/kg/day) in rats, accumulation was found in plasma and tissues due to decreased kidney clearance [6].

Since saccharin has a high polarity, it is expected to be quickly removed from the body with urine. In parallel with this situation, when it is included in the circulation, it is mostly found in plasma, kidney and bladder. Also, it is not covalently bound to DNA [7,8].

In some studies, it has been reported that it may increase bladder neoplasm tumors depending on the dosage taken with the diet. Especially two generation studies made in this sense become more enlightening. The effect of lifetime exposure of a diet containing 5% saccharin with water containing different proportions of ortho-toluene sulfonamide was examined. Increased incidence of bladder tumors has been observed in male rats fed a 5% saccharin diet in both generations [9]. In another two-generation study, sodium saccharin intervention in varying ratios ranging from 1 to 7% was investigated. There was an increase in bladder tumor development with a diet containing 3% and more NaS depending on the dose response. When the dose decreased, a sudden decrease in tumor incidence was observed [10]. In a different study investigating the consumption of different doses of NaS, the body weights of the ancestors who consumed 5% and 7.5% NaS were found to be low when weaned. In addition, bladder neoplasm was observed in those older than 18 months. All malignant neoplasms were found to occur in the group fed with 7.5% saccharin [11].

Considering the reason for the development of bladder tumor in male rats, because they have a urinary system with a pH higher than 6.5, consumption of saccharin in 3% and higher intensity decreases urine osmolality, increases urinary volume and presence of precipitate in urine and causes urothelial damage leading to hyperplasia. However, there is no clear evidence that it causes cancer in humans [12]. In patients with diabetes who are supposed to consume more artificial sweeteners than the general population, cancer risk due to saccharin was not found to be higher [13].

It has also been reported that when used with compounds such as saccharin formamide, l-ascorbate, nitrosamine, caffeine, it is not associated with tumor or cancer development alone. However, it has been reported to contribute to the development of cancer. It was concluded that this was particularly related to the species, tissue and urine pH of the animal [14-18]. For this reason, IARC (International Agency for Research on Cancer) has defined saccharin as a reasonably expected human carcinogen in the Group 3 carcinogen class. There is sufficient evidence for carcinogenicity in experimental animals of sodium saccharin and other saccharin salts, but not in humans. However, the development of bladder tumor is not related to DNA, and it has been linked to the increase in cytotoxicity and cell proliferation of sediments containing calcium phosphate in the urine [5,19].

It has been reported that there is no mutagenic effect and tests related to Na-saccharin causing mutation give negative results. It has been stated that commercial saccharins may cause lesions in the retina and optic nerves by causing teratogenic effect due to the pollution

it contains [2]. In a study conducted by Calorie Control Council, daily saccharin consumption; 0.38 mg/kg BW in men and women over the age of 55, 0.39 mg/kg BW in women and men between the ages of 18 - 54, 0.44 mg/kg BW in children between the ages of 2-5 and 0, It was found to be 40 mg/kg BW [20].

The Food Scientific Committee (SCF, 1977) determined the NOAEL value for saccharin to be 500 mg/kg VA/day. Based on this, EFSA determined the safety coefficient as 200 and determined the ADI value temporarily as 2.5 mg/kg VA [21]. In the later period, various animal studies have reported that carcinogenic effects are not seen in male rats while carcinogenic effects are not observed in other animal species. It was reported that this was due to the urinary system of the rats [1,4,12]. Thus, SCF deemed the elimination of the temporary situation in 1995 and the NOAEL value for saccharin was 1% (500 mg/kg) of the diet; He decided to have an ADI value of 5 mg/kg VA for Na-saccharin. It is determined as 3.8 mg/kg VA as free acid. The allowable amounts for foods are 100 - 200 mg/kg. In 2000, the FDA removed the warning labels for saccharin [12,22,23].

Taste receptors

Various artificial sweeteners and glucose were applied to the subjects together to examine the effect of sweeteners on glycemic control, appetite. There was no difference in the blood glucose response of the saccharin and glucose intervention and in the perception of hunger or satiety according to giving only glucose [24]. In another study, it was reported that saccharine intake caused more saccharin consumption, increased food consumption per kg BW and increased weight and fat tissue [25].

To understand this situation, it is necessary to look at tad receptors. Tad receptors are G protein conjugated receptors containing two subunits of heterodimeric structure. Aspartame and neotame are connected to the T1R2 subunit, and saccharin and acesulfame-K to the T1R3 subunit. Sucralose shares both subunits. The umami tad receptor also shares the T1R3 receptor in combination with T1R1 [26]. Since sweeteners can bind to different receptors, sweeteners affect the formation of sweet taste when used together. Concomitant use of sweeteners that bind to the same receptor Binding to the receptor.

It will reduce the perception of dessert as it will cause the race. However, there may be exceptional situations [7].

Stimulation of intraoral taste receptors leads to the release of α-gustducin, which activates phospholipase C, produces inositol phosphate and intracellular Ca release. This signal enables TRPM5 to activate and taste cells to depolarize. Thus, neural transmission of sweet taste to the brain is carried [26]. Apart from the mouth, sweet taste receptors are also found especially in the small intestine and pancreatic β cells. As in the mouth, the sweet signal causes the release of GLP-1 and insulin. It can also be found in various tissues and cells, such as adipose tissue, leukocytes, lung and bone. It stimulates the release of GLP-1 and GIP (glucose dependent insulinotropic peptide) in the small intestine. Passing into the bloodstream, GLP-1 stimulates the release of insulin and suppresses glucagon release. It increases the feeling of satiety [4,26]. However, it has been stated that consumption of saccharin may increase food consumption by reducing the ability to maintain energy balance in the presence of sweetened food. It has also been reported that its relationship with the gut microbiota may be associated with glucose intolerance, leading to increased energy harvest due to an increase in the glycan destruction pathway. However, cephalic causes a decrease in response. Although it causes relative hypoglycemia when consumed for the first time, this situation disappears in continuous consumption [4,27].

In one study, the glucose tolerance test response of saccharin and glucose was examined and it was seen that there was a significant difference in blood glucose level when taken orally. It has been found to disrupt glucose balance and GLP-1 release, decrease saturation and generate a relative hyperglycemic response [28]. The use of saccharin may impair regulation of glucose control and energy balance, glucose tolerance, insulin release, and glucose absorption [29]. As a result, the body can cause an increase in adipose tissue, hyperinsulinemia and insulin resistance.

Conclusion

According to the latest IARC report (1999), saccharin is not carcinogenic to humans, although there are very conflicting study results. Dietary intake of 1% (500 mg/kg VA) for animals is accepted as NOAEL value, 5 mg/kg VA for saccharin salt and 3.8 mg/kg VA for saccharin acid as ADI value in humans. According to the data calculated from dietary consumption, EDI (estimated daily intake) intake shows that it does not exceed ADI. It has been reported that sugar can replace sugar for individuals who want to reduce their use of sugar, especially in beverages. However, it should be remembered that it may cause glucose intolerance and hyperinsulinemia and ultimately insulin resistance in obese individuals. For people for now Although it is stated that it is not a carcinogen, it should be considered considering its potential carcinogen. If it is to be used, consumption of Na, K and Ca salts should be preferred, thereby ensuring its rapid excretion.

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Volume 15 Issue 3 March 2020