Artificial Sweeteners may Have Adverse Effects on the Human Body

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Abstract. With the increasing attention to people's health, the concept of healthy diet has gradually become popular among the public. Among many processed foods, artificial sweeteners have been favored by consumers all over the world because of their low calories and high sweetness. However, with the deepening of the research on artificial sweeteners, there are continuous research on artificial sweetness. The medicine is not a completely healthy food. Through rat experiments and clinical experiments, researchers from all over the world have verified that ingestion of artificial sweeteners not only promotes drug resistance mutations in human cells, but may also affect the human central nervous system, thus interfering with the normal metabolic process of the human body, eventually causing toxic damage to brain tissue and damage to the hippocampus. Xi and memory, obesity, diabetes, hypercholesterolemia and other metabolic syndromes. In addition to the above adverse effects, there are also research results that show that the intake of aspartame is related to cancer, but the research in this regard has not reached a definite conclusion, so the final result is still controversial, and further clinical trial verification results are needed. This article has sorted out the current evidence that eating artificial sweeteners may have adverse effects on the human body, hoping to provide relevant scholars and consumers with a more objective and rational new perspective, so as to consider the intake of artificial sweeteners more carefully.

Keywords: Artificial sweeteners; drug resistance; obesity; cancer.

1. Introduction

Over the recent years, with the continuous development of the economy and more people are aware of the significance of a healthy life, the topic of healthy eating has become a hot topic in society. Artificial sweetener is a synthetic or semi-synthesized substitute for sucrose. Sucralose, aspartame, saccharin, cyclamate and acesthem potassium are all common artificail sweetenrs. At first, artificial sweeteners, with their extremely low-calorie content and extremely high sweetness, were widely used for diseases caused by excessive intake of sugar or calories such as diabetes and daily diet to help people maintain a healthy weight. However, with the continuous exploration and in-depth research on artificial sweeteners, its disadvantages have gradually emerged. The study found that artificial sweeteners are not only different from people's health, but also cause many adverse effects on the human body, such as may cause changes in cell resistance, affect the normal operation of the central nervous system, cause difficult-to-recoverable toxic damage to brain cells and hippocampus, and affect the learning and memory function of the hippocampus, and then guide It causes metabolic disorders, obesity, diabetes and other metabolic diseases. At the same time, some clinical data show that artificial sweeteners may have the risk of cancer in humans. It can be seen that artificial sweeteners are not ideal sugar substitutes. Clinically, there are dissepons for their benefits and risks. There is still room for further verification of the role of sweeteners in the human body. Therefore, this article discusses the possible impact of artificial sweeteners on the human body from different aspects, in order to provide a certain theoretical basis for clinical scholars to better understand artificial sweeteners.

2. Drug Resistance of Bacterial Cells

Antibiotic resistance (AMR) refers to the tolerance of microorganisms to the original effective antibacterial drugs, so that conventional treatment cannot exert its clinical effect, resulting in long-term illness and even the risk of death. The data shows that AMR kills more than 700,000 people every year and has been recognized as one of the global public health challenges. If the response strategy is not adopted in time, it is estimated that the number of deaths will reach 10 million every year.

The production of AMR is closely related to the transfer of antibiotic-resistant gene (ARG) between bacterial cells. As the main selective pressure to promote ARG transfer, antibiotics not only strengthen the transmission of ARG in cells, but also spontaneously mutate to AMR by targeting bacterial cell components. The study found that a variety of artificial sweeteners, including aspartame, can have a similar antibiotic effect in the intestinal microbiota [1].

In animal experiments conducted by Zhigang Yu et al., mouse fecal bacteria were used as receptors and GFP-labeled Pkjk5 plasmids as extracellular DNA for testing, with sucralose (SUC), saccharin (SAC), acesulose potassium (A) and aspartame (ASP) respectively. The aqueous solution of artificial sweeteners such as CE-K) and the aqueous solution of sucrose and glucose are mixed. The concentration of artificial sweeteners is set to seven (0, 0.03, 0.3, 3, 30, 60 and 300mg/L) at room temperature for 6 hours to detect the fluorescence rate of mouse fecal bacteria. The results showed that when the four artificial sweeteners were 300mg/L, the DNA conversion rate of mouse fecal bacteria increased by more than four times, and the SUC treatment group increased by about 5.1 times. In contrast, the glucose and sucrose groups could not promote the transformation of DNA in the fecal bacteria community [2]. In the experiment to detect whether the permeability of the cell membrane has changed, the experimenters treated the Gram-negative bacteria ADP1 with the above four sweeteners and evaluated the change of cell membrane permeability with the staining rate of iodopropane (PI). The results after 2 hours showed that the bacteria stained by PI increased in a concentration-dependent manner. When exposed to four artificial sweeteners of 300mg/L, the permeability of the bacterial envelope increased by 1.2-1.5 times. However, glucose and sucrose did not significantly change the permeability of bacterial cell envelopes. In addition, experiments have shown that the expression of the AcuG gene, an adhesive induced by aspartame to increase bacterial adhesion, has grown by 1.9 times, and the genes in the N-terminal domain of the relevant transporter also showed an increase [3].

When the permeability of the cell envelope increases and DNA transfer becomes easier, it increases the possibility of cells mutating in the direction of drug resistance, and when there are enough mutated cells, it will affect the drug resistance performance of the whole intestine and even the human body. Once human drug resistance is enhanced, many routine methods of antibiotic treatment will lose their original effect and increase the risk of long-term illness.

3. Effects on the Central Nervous System

3.1. Improve the Level of Pro-inflammatory Cytokines

Cerebrospinal fluid is one of the intrinsic contents in the cranial cavity, which has close material exchange and immune effect with the brain parenchyma and blood circulation. In the central nervous system, cerebrospinal fluid plays a very critical role, including but not limited to supplying nutrients to brain cells, carrying away metabolites of brain tissue, protecting and supporting the brain and spinal cord. Therefore, the stability of the composition and pressure level of the cerebrospinal fluid is pivotal to maintaining the balance of the nervous system. When the cytokines in the cerebrospinal fluid change, it may lead to severe nerve inflammation. The trauma caused by nerve inflammation to the body is often persistent and difficult to reverse, including vascular damage, oxidative stress response, interfering with multiple functions of the human brain and producing toxicity, accelerating brain aging lesions, etc. Existing clinical data also show that the content of MCP-1 (monocyte

chemoprotein), YKL-40 (chitopolyse 3-like-1 protein) and TGF-β (translative growth factor) in cerebrospinal fluid in patients with Alzheimer's disease are higher, and IL-1β (decomposed generation) in cerebrospinal fluid of Parkinson's patients. Xie Su), the level of IL-6 (interleukin 6) is higher, and the levels of il-1βand IL-6 in the cerebrospinal fluid of patients with amyotrophic lateral sclerosis are higher. Therefore, exploring the specific effects of artificial sweeteners on cytokines in cerebrospinal fluid will help assist in the diagnosis of neurological diseases.

In order to solve this problem, Xiaoyi He and others used 96 female rats and randomly divided them into 4 groups. Each group was divided into 12 control groups and 12 ASP treatment groups. They collected cerebrospinal fluid, blood and brain tissue of rats after 1 week, 2 weeks, 4 weeks and 8 weeks later to analyze pro-inflammatory cytokines. The level of IL-6, TNF-α and IL-β. The effect showed from the second week, the levels of IL-6 and IL-β in the brain of the ASP processing group increased significantly ($p<0.001$). After 4 weeks of experimental observation, the water of the three inflammatory cytokines increased significantly on average [4], fully demonstrating the abnormal role of artificial sweeteners in cerebrospinal fluid.

At present, it has been confirmed that brain neurons containing high concentrations of omega-3 and omega-6 which are more susceptible to oxidative degradation or stress response, and aspartic acid and glutamate, the decomposing metabolites of ASP, have neurotoxic effects. Therefore, when brain neurons are exposed to excessive aspartic acid, astrocytes in the brain will be activated, resulting in corresponding injury symptoms. The brain neuron cells are overexcited to produce free oxygen (ROS), which attacks other neuron cells and causes them to degenerate or even apoptosis. Simultaneously, the cerebrospinal fluid is able to establish communication with immune cells via meningeal lymphatic vessels and the peripheral bloodstream. Therefore, when the level of inflammatory cytokines in cerebrospinal fluid increases, the corresponding immune cells in the body fluid will also be stimulated synchronously. Once activated, these immune cells are transported to the lymph nodes via the circulatory system, which triggers the lymph nodes to initiate an immune response. Further produce a systemic peripheral inflammatory reaction.

Fortunately, this kind of inflammatory reaction caused by the consumption of artificial sweeteners is not unable. Haiyuan Ma and others have proved through research that eating vitamin E can effectively improve the survival rate of nerve cells, relieve the apoptosis of glial cells, and play a certain protective effect on the nervous system, so in the day A reasonable intake of vitamins should be in the regular diet to protect the normal functioning of our brain area responsible for learning and memory [5]. However, vitamin E is not effectively relieved of all neuroinflammatory reactions, and the mechanism of action still needs to be further explored clinically.

3.2. Toxic Damage to Neurons and Memory Function Areas of the Brain

As the most abundant neurotrophic factor in the body, BDNF (brain-derived neurotrophic factor) plays a very crucial role in the brain. It can play a role by binding to tyrosine kinase B, including promoting the survival of nerve cells, supporting cell differentiation, acceleratory synaptic plasticity and neurogenesis, especially promoting Neurogenesis of the hippocampus. The hippocampus is an crucial area of the brain responsible for body learning. Ingestion of ASP significantly reduces the level of BDNF in the brain of mice, and multiple pathways that promote brain neurodevelopment and synapse formation cannot be expressed, and the formation of synapses is the basic process of learning and memory of the hippocampus. The function of the hippocampus is disturbed, which will seriously affect daily work and study. At the same time, the reduction of BDNF will lead to the enhancement of the expression of the Caspase-3 gene that promotes apoptosis, and the reduction of the expression of the Bcl2 gene that inhibits apoptosis. The brain neurons are unbalancedly regulated by these two genes, which is more likely to have early apoptosis or large-scale damage. U-pathi's experiments also detected a significant increase in the probability of DNA transcription errors in mitochondria of brain cells.

In addition, COX-2 and PEG2 are important inflammatory factors. Long-term accumulation will lead to enhanced inflammatory response in the cerebral cortex. Therefore, some experiments have pointed out that long-term consumption of ASP can lead to migraine, memory loss, irritability, etc.

Since prolonged dietary exposure to ASP causes a large increase of various neurotoxic metabolic components in the central nervous system,people have become fearful of the potential neurotoxic effects of ASP.Most studies mention that ASP can induce brain cell damage, but the types of damage have not been elaborated. In order to further explore how ASP has a toxic effect on cerebral cortex cells and neuron cells, U-pathi et al. used 19 healthy female rats and divided them into three groups, namely, the normal diet group (5 rats), the low-dose ASP group (7 rats, code-named LA group), and the food Use high-dose ASP group (7 rats, code-named HA group). After 8 weeks, three groups of rats were tested for weight, cyclooxygenase-2 (COX-2), brain-derived neurotrophic factor (BDNF), prostaglandin (PEG2) and other indicators in the cerebral cortex. The results showed that there was no significant difference in body weight and brain weight of the three groups of rats, but compared with the control group, the BDNF levels of the LA group and the HA group decreased significantly, and the water average of COX-2 and PEG2 in the HA group increased significantly. The researchers also detected a important increase in the expression of the Caspase-3 gene and emergency oxidation response markers in the cerebral cortex [6].

Therefore, in order to better protect the health of our central nervous system and brain cells, the intake of ASP should be reduced as much as possible.

3.3. Cause Obesity and Other Metabolic Diseases

As one of the most common health diseases in life, the number of people suffering from obesity in the world is increasing year by year, especially among teenagers. In addition to physical overeating, lack of exercise, depression, family inheritance and other factors, the causes of obesity are also closely related to the circulation metabolism in the human body and the health of the nervous system. Many studies in recent years have shown that the intake of artificial sweeteners can affect the blood circulation and metabolic process of the human body, so that it is impossible to maintain a healthy weight.

Human sweet receptors (STRs) are mainly composed of three G protein-coupled receptor families (T1R1, T1R2, T1R3). In Katsumi lizuka's experiment, the researchers randomly divided 50 healthy rats into 10 groups, feeding them into normal diet and high-fat drinks respectively. In the case of eating, drink water at concentrations of 2.5% and 10% fructose aqueous solution, and sucralose aqueous solution with concentrations of 0.01% and 0.015%. After 12 weeks, the weight of these rats, calorie intake and the expression of sweet receptors in the body are tested. Rats who eventually ingested sucralose significantly increased their weight than rats who consumed water and fructose, increased calorie intake, and significantly reduced the expression of sweet receptors TIR2 and T1R3 [7]. When the expression of STRs decreases, the brain's ability to capture glucose weakens, and the threshold of glucose-induced neurons increases, which weakens the fullness effect of glucose. Therefore, we have to make up for the low glucose sensitivity by increasing calorie intake.

At the same time, the intake of artificial sweeteners may also reduce the brain's sensitivity to insulin. Some scholars suggest that eating drinks containing sweeteners and other sugars at the same time will quickly reduce the insulin sensitivity of rodents and the sensitivity of the brain's sweetness center. An animal experiment randomly assigned 45 healthy experimenters to (1) drinks containing sucralose and other sugars; (2) drinks containing sucrose and other sugars; and (3) drinks containing sucralose, other sugars and maltodextrin. The experimenters will be tested in two weeks. The results showed that the brain response of the (3) group of experimenters to sucrose became slow and the insulin sensitivity decreased, while the experimenters of group (1) and (2) did not change, which further verified the previous views [8]. Because when sucralose is combined with the sweet receptors T1R2 and T1R3, the expression of sodium-glucose cotransporter (SGLT-1) in the human body increases, the ability to transport glucose becomes stronger, and the neurons related to sweetness in the brain will secrete more dopamine hormone when stimulated by excessive glucose. Excessive

dopamine will not only affect multiple functional areas, including the prefrontal lobe of the cerebral cortex, but also expand the transmission of neural electrical signals between cell synapses. When the brain is affected by high-intensity neurotransmitters for a long time, the impact of normal hormone levels on the brain is weakened, that is, the brain's sensitivity to dopamine gradually decreases.

When humans are unable to digest more food, excess calories will be converted into fat stored in the body, which will eventually lead to obesity. Obesity is not only a disease, but also a variety of diseases such as hyperlipidemia, hypertension, diabetes, metabolic syndrome, and cardiovascular diseases. At the same time, in this era of increasing attention to healthy body shape, the psychological burden caused by obesity on patients cannot be underestimated.

4. Effect on Cancer

Nowadays, the concept of "low-calorie" diet is respected. In the past, artificial sweeteners were a common substitute for added sugars in the worldwide food market. Some studies have found that there may be a link between artificial sweeteners and cancer. However, there is still no definite conclusion about the specific effects of artificial sweeteners in different cancers, so the relationship between artificial sweeteners and cancer is still controversial.

In order to further investigate the impact of artificial sweeteners on cancer, Charlotte Debras et al. conducted an 8-year study, which divided the 10,865 experimenters into three groups according to the consumption of artificial sweeteners: non-consumers, low consumers and high consumers, mainly tested Changes in the consumption of three artificial sweeteners, ASP, acesulam potassium and sucralose, on their risk index (HR) for breast or prostate cancer. All experimenters were tracked back for an average of 7.8 years under the condition that other influencing factors were excluded as much as possible through back adjustment, and 3,358 cancer cases were finally diagnosed [9]. That is, the intake of artificial sweeteners is positively correlated with the overall cancer risk. The HR index of high artificial sweeteners is 1.13 times higher than that of non-consumers. In particular, the cancer risk index of experimenters who ingests ASP (HR=1.15) and acesum potassium (HR=1.13) is higher, and the risk of cancer is Upward trend. In addition, overweight and metabolic disorders are also one of the important factors that promote cell cancer.

Regarding the effect of ASP on human colorectal cancer cells, Maghiari et al. observed the toxicity of ASP to HT-29 cells. By cultivating HT-29 cells for 72 hours in a medium containing 0.1, 0.25, 0.5, 1, 3, 6, 15, 30 and 50mm concentrations, respectively, the cytotoxicity and the number of living cells were finally detected [10]. Their results show that HT-29 cells show signs of toxicity from the concentration of 0.5mm, and with the increase of test concentration, the signs of toxicity become more and more obvious. The percentage of detected living cells decreased significantly, from 79.35% of 15mm to 25.01% of 50mm. This result shows that ASP does have dose-dependent toxic effects on HT-29 cells.

On the contrary, Anna Palomar-Cros and others gave different results by using MCC-Spain to study the group experiment of ingesting artificial sweeteners from different groups of people. The researchers divided the experimenters into two groups of A and B according to whether they ingested artificial sweeteners, and then divided group B into (a) low intake group, (b) medium intake group and (c) high intake group according to different intakes of artificial sweeteners. After a period of time, observe the effect of different artificial sweetener intake on the cancer rate. The results showed that there was no direct link between the intake of ASP and the likelihood of cancer in those who did not have diabetes.However, for patients who with diabetes, the results show, ingestion of aspartame or other artificial sweeteners may be associated with their risk of developing stomach cancer, and a large intake of artificial sweeteners other than ASP may also lead to an increased risk of colorectal cancer [11].

Similarly, Brendan J. Guercio et al. analyzed the data of 1,018 patients with stage III colon cancer. By investigating the relationship between the intake of artificial sweetener drinks and the recurrence

rate and mortality of cancer, they finally concluded that the replacement of 12 ounces of sugary drinks with artificial sweetener drinks will reduce the risk of cancer recurrence and death. 23% [12].

In addition to the above research, there are still many conjectures about how ASP causes cell cancer, which is still in the verification stage. Because of the completely different results, the possible carcinogenic phenomenon of artificial sweeteners still needs to be further explored in the future. But there is no doubt that the use of artificial sweeteners needs to be judged more strictly.

5. Conclusion

According to existing literature research, eating artificial sweeteners may cause damage to the human body, such as stimulating human intestinal cells to undergo drug resistance mutations, causing the human body to develop resistance to antibiotics; stimulating the central nervous system to produce inflammatory reactions, causing toxic damage to brain nerve cells, and disrupting many areas of the brain. The normal function of the domain also accelerates the aging and apoptosis of cells in the body, eventually leading to a series of metabolic diseases such as obesity, diabetes, hypercholesterolemia, etc. However, the current research results on whether the consumption of artificial sweeteners will cause human cell carcinoma is variant, and there is a lot of controversy, which needs to be further explored. The above experimental results further prove that artificial sweeteners do have advantages, but they are not as healthy as people previously thought, and excessive intake may lead to the occurrence of many diseases. Therefore, it is particularly important to guide the public to correctly recognize the impact of artificial sweeteners on health and strictly control the daily intake of artificial sweeteners, especially for children, pregnant women and patients with chronic diseases. We should reduce our dependence on artificial sweeteners and pay attention to the potential harm caused by excessive intake of sugar substitutes, through reasonable Dietary structure and exercise to maintain health. At the same time, most of the current research is animal research, which cannot be well combined with clinical practice. In the future, we should focus on strengthening clinical research, taking into account ethical factors, and further explore the correlation and specific mechanism of artificial sweeteners with different tissues and organs of the human body on the basis of existing results.

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