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Aspartame: A Sweet Toxin?

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Abstract

L-aspartyl-L-phenylalanyl-methyl ester, commonly known as aspartame, is one of the most widely used and controversial sweeteners. Many have questioned the safety of this chemical, concerned that it may be neurotoxic and carcinogenic. Numerous studies have been conducted on the three basic constituents of aspartame: aspartic acid, phenylalanine and methanol; scientists have tried to determine whether the ingestion of aspartame will cause a significant increase in blood plasma levels of these chemicals, and whether such an increase is dangerous. This review analyzes various studies conducted on the health effects of these metabolitic byproducts of aspartame.

Introduction

Consumers were thrilled when aspartame was introduced to the market. Since this artificial sweetener's safety was approved, it has found its way into over 6,000 products, including soft drinks, chewing gum, hot chocolate, candy, desserts, sweeteners, and yogurt. Sold commercially under names such as Nutra-Sweet, Equal and Canderel, aspartame is two hundred times sweeter than sucrose. Although it has the same number of calories per gram as sucrose, people generally use less of it, consuming fewer calories (Soffritti et al. 2006).

The discovery of aspartame was accidental. In 1965, James M. Schlatter discovered this chemical as he was trying to produce an anti-ulcer drug candidate for G.D. Searle & Company. Some aspartame spilled on his hand, yet he did not wash it off, believing that it was not toxic. He came to recognize its sweetness when he licked his fingers in order to pick up a weighing paper. Despite its unintentional discovery, aspartame has had a profound impact on the dieting habits, and it is one of the most widely used artificial sweeteners in the world (Sofffritti et al., 2007).

Aspartame's unique formula helps obese maintain their weight loss programs and allows diabetics to enjoy exceptional dishes within their dietary restrictions (Butchko et al. 2002). In the United States, the acceptable daily intake (ADI) of aspartame is 50 mg/kg body weight. Consumption by the general population ranges from 2 to 3 mg/kg body wt, and the average consumption by children and women of child bearing age has been estimated at 2.5-5.0 mg/kg bw/day (Soffriti et al., 2007).

Extensive research was done on the safety of aspartame before it entered the market. Various studies were conducted with a number of human populations in order to determine its safety; research

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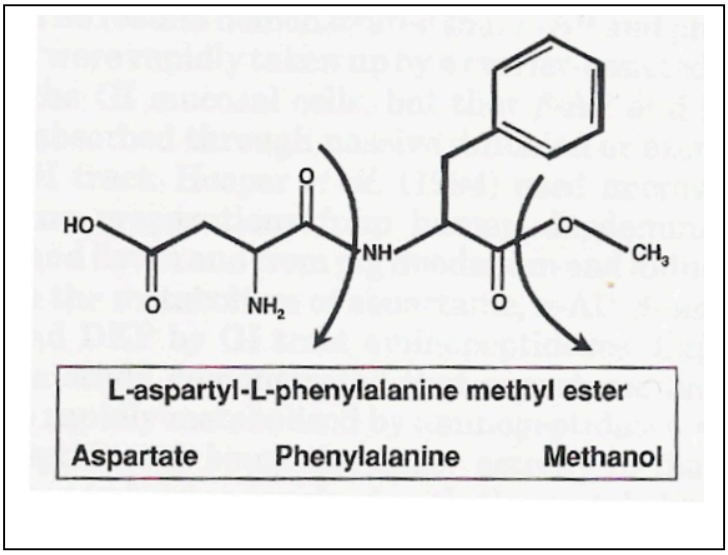
exists about its safety. Numerous anecdotal reports were released subsequent to aspartam's approval describing the adverse health affects associated with it. Written complaints include that of dizziness, visual impairment, disorientation, ear buzzing, tunnel vision, loss of equilibrium, severe muscle aches, numbing of extremities, increased blood pressure, retinal hemorrhaging and depression (Monte 1984). Even more serious is the startling rise in brain tumor rates since the introduction of aspartame to the market (Olney et al. 1996).

FDA Approval

Aspartame was approved by the FDA for use in solid foods in 1981, in soft drinks in 1983, and as a general sweetener in 1996. The FDA denied approval of this sweetener for eight years before allowing it on the market since researchers had discovered that the ingestion of aspartame yielded toxic effects. A Public Board of Inquiry (PBOI) convened in 1980 to review the research of G.D. Searle and Company and they denied approval of the chemical due to lack of sufficient evidence proving that aspartame did not cause cancer. The FDA commissioner, Arthur Hull Hayes, established another PBOI in 1981. This board did not reach a consensus regarding the chemical, yet the commissioner overruled his own board of inquiry and approved the food additive. Conspiracy theories brew because Hayes left the FDA in 1983 to join the public relations department of Searle (Whitmore 1996). The validity of the FDA's approval is further questioned when the research conducted on aspartame is analyzed. One is compelled to question the design efficiency of many studies when one notes that 100% of the 74 industry-funded studies found no problem, while 83 out of 90 non-industry funded studies found one or more problem with aspartame (Warner 2006).

Structure and Components of Aspartame



Aspartame is a dipeptide which has the formula L-aspartyl-L-phenylalanyl-methyl ester (Maher and Wurtman 1987). Upon ingestion, aspartame is metabolized in the gastric tracts to its three constituents: aspartate, phenylalanine, and methanol. These components proceed to be transformed into other products. Aspartate is transformed into alanine and oxaloacetate; phenylalanine is transformed into tyrosine, phenylethylamine and phenylpyruvate, and methanol is transformed into formaldehyde which later forms formic acid (Soffritti et al. 2006). While these components are commonly digested, concerns have been raised about their safety when they are metabolized after aspartame ingestion.

Aspartate

Aspartate is an extremely common, non-essential amino acid. It is usually rapidly metabolized by the body and subsequently incorporated into proteins and utilized for energy. This amino acid is found in large concentrations in natural products; 100g of chicken yields 2600 mg of aspartate whereas a 355 ml beverage sweetened 100% with aspartame only provides 70 mg of aspartate. Furthermore, a glass of no-fat milk provides 13 times as much aspartic acid as a beverage sweetened 100% with aspartame (Monte 1984).

While aspartate is not toxic when absorbed, even in large quantities, from natural foods, it may be harmful to the body when it is absorbed after the consumption of aspartame. Blood component levels of amino acids such as aspartate and phenylalanine will not rise significantly after the digestion of natural proteins. Due to their quaternary structures, natural proteins are digested slowly and enzymes must catalyze the protein and release numerous amino acids before phenylalanine or aspartate can be released. On the other hand, the digestion of aspartame can raise component blood levels rapidly since the chemical only requires the breakage of two bonds for absorption (Monte 1984).

When aspartate it is absorbed in excess, it can wreak significant damage on the body. Daabes and co-workers (1985) determined that plasma levels of aspartate and glutamate which exceeded 110 numol/dl, induce hypothalamic neuronal necrosis in neonatal rodents. Later, Olney and Sharpe (1969) conducted a similar experiment on non-human primates. They delivered large boluses of glutamate, a similar dicarboxylic amino acid, and found that it led to hypothalamic neuronal necrosis. Furthermore, scientists have found that high plasma levels of this amino acid cause endocrine disorders in mammals, leading to the release of pituitary gonadotropins and prolactin in the rhesus monkey and noticeably elevated plasma levels of luteinizing hormones and testosterone in rats (Monte 1984).

Experiments have determined that aspartame alone will not elevate plasma aspartate levels for an extended time period. However, concerns have been raised about the ability of aspartame to spike plasma aspartate levels when it is ingested in conjunction with mono sodium glutamate (MSG). The ingestion of MSG has been known to cause adverse symptoms in individuals due to the substance's neuroexcitatory activity (Reif-Lehrer 1976). Since both aspartate and glutamate are structurally similar,

and pose a threat of neurotoxicity at high dosages, Olney (1982) has suggested that consuming aspartame along with foods which contain MSG leads to a risk of toxicity and of focal brain lesions. However, Stegink and coworkers (1983) conducted numerous studies and discovered that while MSG consumption will lead to a significant increase in glutamate aspartate concentrations when consumed alone, the addition of aspartame to MSG will not cause any further increase in dicarboxylic amino acid levels. Thus, they concluded that is impossible for humans to ever consume enough MSG and aspartame to raise plasma concentrations to those associated with rat neurotoxicity.

Phenylalanine

Phenylalanine is an amino acid which is beneficial for one's health, and can be found in protein-containing foods such as non-fat milk and fruit juice. This amino acid can be lethal to those who suffer from phenylketonuria (PKU), a rare genetic disease. The diets of phenylketonurics are extremely restricted from shortly after birth in order to avoid the risks of mental retardation or various degrees of cognitive impairment (Butchko et al. 2002). However, phenylalanine is not only dangerous for phenylketonurics; spikes in plasma phenylalanine levels can be toxic due to the body's method of uptake of this amino acid.

Upon ingestion, phenylalanine is absorbed across the gastrointestinal mucosa into portal circulation. Most dietary phenylalanine goes unchanged into systemic circulation and is taken up across the blood-brain barrier and into the central nervous system via a transport system that is specific for large neutral amino acids (LNAA). The amount of amino acids which enter and leave the brain is determined by the concentration of the LNAA and their specific affinity constants to the carrier system (Fernstrom and Wurtman 1997). The danger of spiked plasma levels of phenylalanine lies in the fact that it will interfere with the availability of tyrosine and tryptophan. Consequently, phenylalanine will act as a competitive inhibitor of the enzyme tyrosine hydroxylase. This, subsequently, lowers the concentration of brain catecholamine and serotonin, which, in turn, mediates neurological changes and induces seizures (Maher and Wurtman 1987).

Some researchers suggest that aspartame ingestion poses a risk because it provides phenylalanine without other LNAA. Consequently, upon being metabolized there will be an increased phenylalanine uptake by the brain causing the aforementioned problems (Maher and Wurtman 1987). However, other scientists, such as Stegink and coworkers (1987), found that this is not the case. In their studies, they found that the changes in phenylalanine LNAA in normal subjects was no greater than those occurring under normal dietary conditions. This idea was reinforced in a study conducted by Koeppe and coworkers (1991). In this study, positron emission tomography was used in order to observe the effects of elevated plasma phenylalanine levels after the consumption of large boluses of aspartame. An 11.5% decrease in amino acid transport rate constant was observed along with a 6% decrease in tissue distribution volume of aminocyclohexanecarboxylate. Thus, under normal dietary use, aspartame is unlikely to cause changes in brain amino acid uptake which would be measurable by PET.

Despite the fact that many scientists do not believe aspartame will negatively affect the brain's uptake of amino acids, several adverse side effects are observed after phenylalanine's digestion. Many individuals have reported that they have suffered from neurological or behavioral reactions in association with aspartame consumption, a symptom which can be linked to increased phenylalanine levels (Maher and Wurtman 1987). Furthermore, Walton and coworkers (1993) found that individuals with a history of mood disorders, such as depression and bipolar, exhibited stronger symptoms after consuming aspartame. They hypothesize that the disorders are exacerbated by aspartame's phenylalanine component which upsets the balance of neurotransmitters.

Another concern raised regarding phenylalanine is its ability to induce seizures. In one study, mice were given dosages in which phenylalanine levels rose above tyrosine levels, a phenomenon which will occur after any aspartame dose in humans. Subsequently, the mice were introduced to epileptogenic drugs, inhaled fluorotyl or electro convulsive drugs; the frequency of seizures following these treatments was greatly increased due to increased plasma phenylalanine levels (Maher and Wurtman 1987). Some researchers disagree with these findings. In research done by Dailey and coworkers (1989), acute oral doses of aspartame, ranging from 0 – 2500 mg/kg were administered to CD-1 mice. Increases in phenylalanine and tyrosine and modest reduction in brain serotonin and 5-hydroxinol acetic acid were observed. However, these changes were insufficient to cause functional deficits which might have the capacity to facilitate pentyl enterazol-induced seizures. Thus scientists have not been able to conclusively determine whether or not aspartame will induce seizures.

Methanol

Methanol, or wood alcohol, is the simplest alcohol with the formula CH_3OH. Occurring naturally in fruit juices and alcohol, it can be found in considerable quantities in a daily diet; for instance, tomato juice provides six times more methanol than an equivalent amount of beverage sweetened 100% with aspartame (Butchko et al. 2002). Ten percent of aspartame's weight is absorbed as methanol. This chemical is released in the small intestine after chymotrypsin hydrolyzes the methyl group of the dipeptide. It is transformed later into formaldehyde and formic acid., both toxic metabolites. Absorption of methanol increases if it is ingested as free methanol, such as in heated foods and soft drinks (Monte 1984).

The dangers of methanol consumption via aspartame have been raised over the years. Methanol does not cause toxicity when consumed in wines and juices because of the beverages' natural protective features. For instance, juices and wines contain high ethanol to methanol ratios; some neutral spirits contain 200 molecule of ethanol per molecule of methanol and orange juice contains 0.8 mg/L of methanol and 380 mg/L of ethanol. This has a protective effect since ethanol slows the rate of methanol being transformed into formaldehyde, thereby allowing the body to excrete methanol in breath and in urine. Juices have an added protection since they have high osmolality and an average caloric density of 500 kcal/L, which also puts definite limits on consumption level rates of methanol.

Since aspartame is not limited by calories or osmolarity, daily methanol levels may rise to unprecedented levels, and may prove to be a cumulative toxin (Monte 1984).

One of the key concerns about methanol is its production of the methyl alcohol syndrome. This toxicity is found only in humans because man has limited biochemical pathways for detoxification. For twelve to eighteen hours after the methanol consumption there is a latent period, followed by severe acidosis which is caused, in part, by formic acid formation. Patients complain of confusion, lethargy, and impairment of articulation, and may also suffer from back pain, vertigo, abdominal pain, labored breathing, leg cramps, and visual loss. There are also fatal cases in which the liver kidney and heart show parenchymal degeneration and the lungs display desquamation of epithelium, edema, emphysema, congestion, and bronchial pneumonia (Monte 1984).

The danger of methanol is rooted in its production of formaldehyde, a known carcinogen. Formaldehyde has been proven to form squamous-cell carcinomas when inhaled by experimental animals. It reacts with DNA causing irreversible denaturation and can interfere with DNA replication, thus causing mutations (Monte 1984). Studies have verified that formaldehyde accumulates after the consumption of aspartame. Trocho and coworkers (1998) synthesized aspartame using a methanol group which had radioactive C-14 and fed it to mice. They later found that the methanol had accumulated in plasma and in the liver, and was bound to protein, thus determining that aspartame contributes to the formation of formaldehyde adducts and its affects are cumulative Not only does aspartame metabolize to form formaldehyde, but it even intensifies the toxicity of this chemical. Forty percent of aspartame breaks down into excitotoxic amino acids, and formaldehyde's toxicity increases when it is in the presence of high levels of free radicals (Saito et al. 2005).

One of the dangerous consequences of methanol absorption is the increased risk of developing lymphomas and leukemias. A case-control study in Argentina discovered that urinary tract tumors (UTT) were directly correlated with aspartame consumption. The risk of UTT was significantly increased in long-term aspartame users compared with non-aspartame users (Andreatta et al. 2008). Another long-term study which studied the affect of aspartame consumption on the incidence of tumors took place in Italy. Soffritti and coworkers (2007) observed Sprague Dawley rats from eight weeks of age until natural death. They observed a statistically significant increase in the incidence of malignant tumors among rats that had ingested aspartame. These tumors included lymphomas, leukemia, preplastic, neoplastic, and lesions of the renal pelvis and ureter. Since rodents have been found to be consistent predictors of human cancer risks, they conclude that aspartame is a multipotential carcinogenic compound whose carcinogenic effects are evident even at daily dose of 20 mg/kg bw.

Despite the compelling evidence, some researchers do not believe that methanol will cause toxicity in humans when ingested in the form of aspartame. They assert that the alcohol is absorbed in such minimal levels that it will be unlikely, and even impossible, to reach levels of toxicity associated with cancers and lymphomas (Butchko et al. 2002). Nonetheless, there are still significant concerns with aspartame's production of formaldehyde.

Conclusion

The results and conclusions of the different studies about the safety of aspartame are spread over a large spectrum; views range from those who claim that aspartame is absolutely safe to those who claim that it is toxic. Research is centered on the possible risks associated with the ingestion of each of aspartame's constituents. Regarding aspartate, many claim that high levels of this amino acid can induce neuronal necrosis and endocrine disorders. A large group of scientists believe that the ingestion of aspartame can lead to dangerous spikes in aspartate plasma levels when eaten in conjunction with MSG, while many others believe that such a spike is impossible.

The debate about phenylalanine's toxicity revolves around the ability of this amino acid to interfere with LNAA at the blood-brain barrier. Some researchers are concerned that this constituent can exacerbate mood disorders and induce seizures. However, the issue is still debated, and many scientists have determined that aspartame's phenylalanine will not cause adverse effects.

Methanol consumption has raised significant concerns since this alcohol is metabolized as formaldehyde, a known toxin. Long-term studies have proven that the methanol component of aspartame has caused lymphomas and leukemias in rats. Nonetheless, other scientists debate these results and claim that typical ingestions of aspartame will not cause toxic effects.

Summary

Aspartame is one of the most controversial sweeteners. The pro-aspartame camp presents data that shows that the ingestion of this sweetener does not lead to significant negative health effect. They claim that the negative studies on lab animals are run with high concentration of materials that will never be present during normal consumption. On the other hand, the anti-aspartame camp believes that the fast digestion of aspartame leads to the concentration of its constituents in the body, causing toxic effects. Clearly, more research must be conducted on the subject in order to conclusively determine whether aspartame is harmful or not. In the interim, it would be advisable that people who are susceptible to metabolic conditions which are possibly affected by aspartame should try to avoid significant consumption of the sweetener.

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