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REVIEW ARTICLE

Artificial sweeteners: Worth the risk, aspartam and alzheimer's disease

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INTRODUCTION

Sugarcane was being used to fatten pigs in early centuries. It was firstly evolved in Papua New Guainía, then spread from there to the rest of the world slowly, after Brazil harvested huge amounts of sugarcanes, to commercialize it. Then, as sugar was introduced into the industry in 16th century, it became one of the most popular and valuable crop in the world. Drinking tea and coffee with added sugar, was an indication of being an elite. The popularity eventually lead to excessive use of the sugar. Thus, this added more pressure on health issues along it. Obesity, dementia, cardiovascular diseases had increased in countries, where sugar based carbohydrate consumption became dominant. But, after a while planting sugarcanes and harvesting the crops became very time consuming and expensive at larger scales, due to the larger demands. Thus something that would give people, the same taste and faster production, seemed eminently attractive. Recent studies have proved that, the continuous consumption of artificial sweeteners have adverse effects on the hippocampal area of the brain, which is responsible for learning and memory (1). This article will cover, how aspartic acid that is a metabolite of aspartame artificial sweetener, effects the brain and is associated with Alzheimer's disease.

Aspartame has a molecular formula of $C_{14}H_{18}N_20_5$. It is composed of 50% of phenylalanine (Phe) , 40% of aspartic acid or aspartate (Asp) in other words and 10% of methanol.

Aspartame was discovered by James Schalleter in 1960s, while he was working on the treatment of gastric ulcer. The solution he had prepared splattered around his desk by mistake, he cleaned up his desk and continued his experiments, when he wanted to turn the page of his book, he licked the tip of his finger and felt a sweet taste in his mouth. He then, worked on that solution and came up with aspartame. Aspartame is made by 2 steps, as follows; fermentation and synthesis. In fermentation process, basic amino acids are produced that are L-Phenylalanine and L-Aspartic acid, that are necessary to synthesize the aspartame.

This is done by bacterial fermentation within the tanks that contains nutrients and seed. The growth of bacteria takes place fast due to ideal conditions, and produces more amino acids. Amino acids get separated from bacteria by centrifugal separation. Then the desired amino acids are separated by ion column exchanger. Figure 2 below illustrates this step.

The second step of producing aspartame is called the synthesis step

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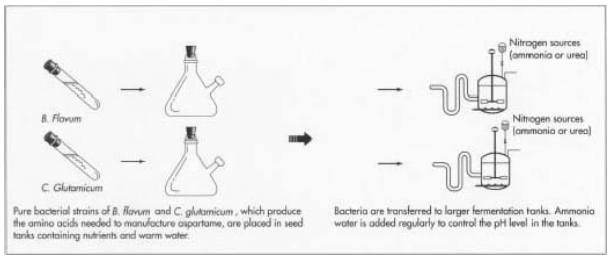

Figure 1. Fermentation Step of Making Aspartame (HowProducts, 2010)

Here, the produced amino acids from first step are modified. The phenyalanine that was produced by fermentation, was modified by adding methanol to it, to make it L phenylalanine methyl ester. These amino acids are then put into a mixing tank of 65 °C for 24 hours. The products were cooled down to -20 °C, thus gets crystalized. The crystals formed are a form of aspartame, by reacting the crystals with acetic acid, and recrystallizing aspartame powder is synthesized. From figure 3, these can be visualized well.

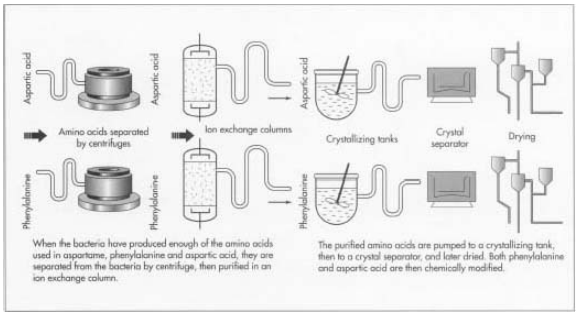

Figure 2. Synthesis Step of Making Aspartame (HowProducts, 2010)

Alzheimer's disease

Alzheimer's disease (AD), is a neurodegenerative disease, which, most of the time leads to dementia. Dementia is progressive cognitive declination that leads to disabilities in patients' behavior and social life (2). The first person who described AD was Alois Alzheimer, said that AD is not a common disorder (3). However, recently in 21st century the prevalence rate of the disease has increased eminently. As it was reported by Nui, the disease's prevalence rate was found to be 5.09% in 2017 Europe (4) The disease is mainly seen in elderly, of 65 years old age and above. Khachaturian mentioned that every one person out of six person who are above 65 years old are having under the risk of having dementia (5).

It was also reported that every five years of age increment, the possibility of getting dementia was doubling (2).

Although the reason behind, why brain cells which store, keep information and responsible for memory and learning, undergo degeneration is not yet known for sure, there are 2 hypothesis scientists come up with; either beta amyloid or tau proteins causing this degeneration (6).

Beta Amyloid & AD

Amyloid precursor protein (APP) is an integral protein, that is mainly found in neurons and the synapses. Its function is not known, but scientists believe, it plays a role in brain plasticity. According to the way the large APP is cut, it forms different types of pieces, and one of the forms is called the beta amyloid. Usually APP gets cut by alpha and gamma secretase enzymes and the chopped off peptides are soluble and can be degraded. However, if APP gets cut by beta-secretase enzyme, the left over fragment is not soluble and form amyloid beta monomer (7).

The reason why scientists tend to believe beta-amyloid could be one of the reasons causing AD, is because, when an AD patients' brain cells were studied, excessive levels of beta-amyloid were observed (6). The following figure 3 illustrates the steps in the formation of beta-amyloid sheets. APP cuts in a specific way to form beta sheet monomers, as they accumulate in small amount, they form oligomers.

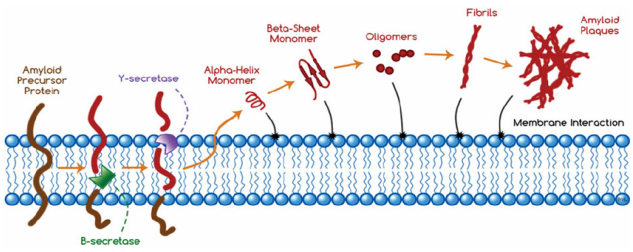

Figure 3. Steps of Beta-Amyloid Sheet Formation (8Drolle, 2014)

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As the clusters of the small accumulations gets larger, they form fibrils and fibrils come together to form, what's called the beta-amyloid plaques.

The beta amyloid plaques that are formed, accumulate around and in between the neurons, thus disabling the message to be passed from one neuron to the other. Basically blocking the communication between the neurons.

Another evidence scientists use to support the hypothesis of beta- amyloids causing AD and eventually dementia is the study done on down syndrome patients. The chromosomes which carries the APP gene, are present more in down syndrome patients (three in numbers). 75% of the down syndrome patients get AD, after they hit the age of 65 (8). Which could indicate that APP and AD are highly associated with each other. Thus making beta amyloid associated with AD as well.

Tau & AD

Tau is a protein that is linked with the microtubules. Its function is to keep the neurons in shape and help in transportation of the messages through neuron. For the tau protein to be able to function well, they need to be phosphorylated, every tau molecule must contain 3 moles of phosphate. In case, this is done in excess that causes the activity of protein to be lowered. In AD patients, tau proteins are hyper-phosphorylated and thus neuro-fibrillated tangles are formed (9). When neurons are neuro-fibrillated, it damages and even leads the neuron cells to undergo apoptosis. The figure 4, below illustrates the tau protein gets hyper phosphorylated, and this leads to the formation of unstable microtubules and clumps of neuron fibrillated tangles.

Oxidative Stress & AD

Oxidative stress is said to be another possible reason causing Alzheimer's disease. Scientists claim that reactive oxygen species and free radicals causes a state called oxidative state, which is responsible for apoptosis.

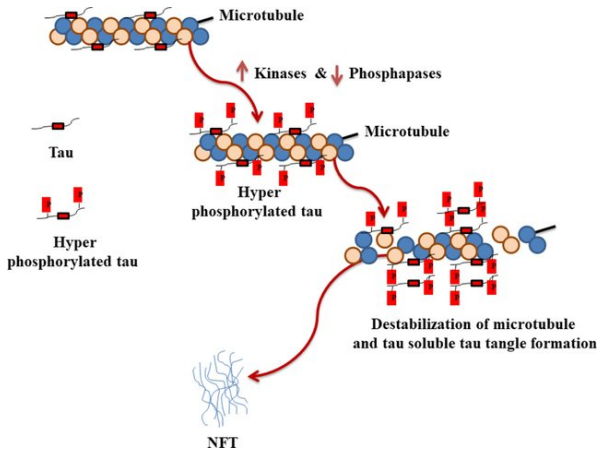

Figure 4. Tau Formation (Kumar,2017)

These free radicals are also said to be responsible of modifying DNA basepairs. The most prone area of the brain to get damaged from these formed oxidative species, is the hippocampus and amygdala (10). That's why, oxidative stress is being associated with AD. Because once the hippocampus and amygdala is disrupted and inflamed due to these species formed as a result of oxidative stress, cells start to die slowly which are responsible for the memory and learning part of the brain.

The figure 5 below shows the oxidative stress and what happens if they lead to mitochondrial dysfunction in brain, as described in paragraph above and this eventually causes neurodegeneration.

Alzheimer's disease & aspartic acid

When an artificial sweetener containing aspartame is ingested, aspartame gets metabolized into three metabolites of phenylalanine, aspartic acid and methanol.

These metabolites have adverse effects and the ability to degenerate the neurons on the hippocampal area of the brain. The neurodegenration, especially in hippocampal area leads to memory losses, cognitive impairment and eventually to AD and dementia. In this section, aspartic acid and its association with AD will be discussed.

Aspartic Acid

40% of aspartame, contains aspartic acid. Aspartic acid has $C_4H_7NO_4$ molecular formula. It is one of the two acidic amino acids, glutamate being the other one.

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It's a non-essential amino acid which can be obtained through diet and used in protein synthesis as well as in neurotransmission. There are two enantiomeric forms of aspartic acid, as L-aspartate and D-aspartate (11).

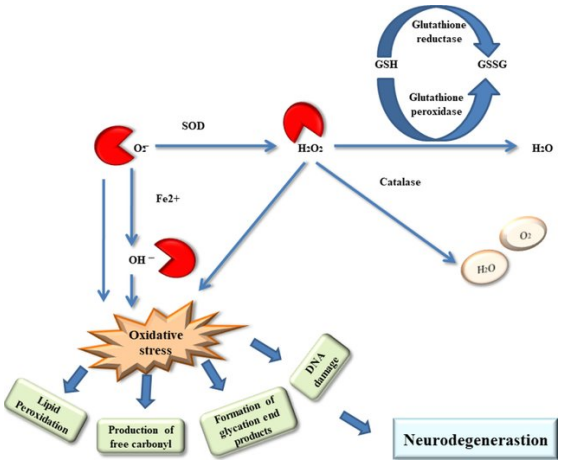

Figure 5. Oxidative Stress in AD (Kumar, 2017)

The figure 6, below shows the CA1 and CA3 regions of the hippocampal cell layer of the rat brain. Picture A and B, shows the rats that were not introduced to aspartic acid and their neurons are health and in proper shape. While pictures C and D illustrates the hippocampal cell layer of the rats, with continuous consumption of aspartic acid. As seen, the neuronal cells are lost in shape, damaged and some of them even went under apoptosis (1). This indicates how aspartic acid is causing neuronal death and may be associated with AD.

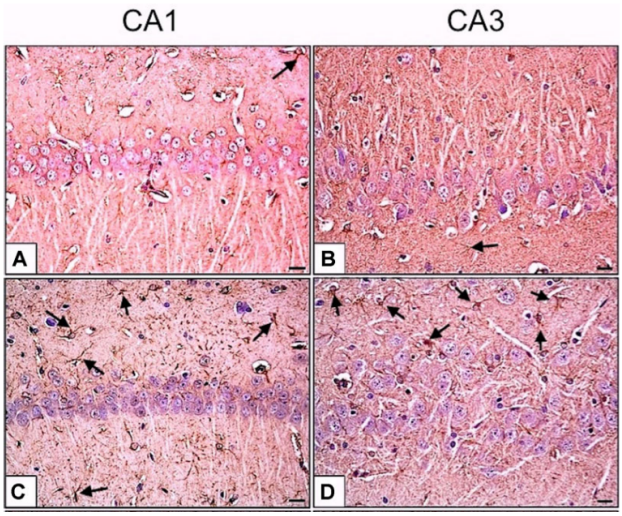

Figure 6. Comparison of Hippocampal Cell Layers of Rats of Normal and Aspartic Acid Introduced Ones (Katip, 2018)

Aspartic acid as excitatory neurotransmitter

Aspartic acid can act as an excitatory neurotransmitter, that activates several receptors like N-methyl- D- Aspartate (NMDA), that is responsible for brain plasticity. This in return causes excitability and leads to neuro-degeneration of neuronal cells, that is the main suggested mechanism behind Alzheimer's disease (12).

Many receptors are responsible for transmitting the neuronal messages and functions in synapses (13). There are different types of ionotropic receptors called NMDA, α- amino- 3- hydroxy- 5- methyl- 4- iso xazolepropionic acid (AMPA) and Kinate receptors. These binding sites are coupled with ion channels, if the sites are polarized, NMDAR is inactive because of the blocked ion channels. If the polarization is disturbed, the ion channels open up and the receptors get activated. Aspartic acid, for instance depolarizes the binding sites, thus activates the receptors (14). However, some of the receptors such as NMDA, can get activated through responding to agonist. "Agonist means, a substance that acts like another substance to stimulate a receptor" (15).

The receptors mentioned are called the excitatory amino acids (EAA) receptors which are mainly present in cortex and hippocampus area of the brain. When these EEA receptors are activated excessively, then it causes neuro-degeneration (14). Aspartic acid has activity at glutamate receptors (11). Figure 7 below, also shows how aspartic acid, a metabolite of aspartame artificial sweeteners, effects the glutamate receptors in presynaptic region.

As aspartic acid increases, it induces the glutamate formation. So decreased levels of glutamate and increased levels of aspartic acid is seen in temporal cortex in people who have AD (16).

In presynaptic region the glutamate cant bound to the glutamate receptors because of aspartic acid competition. The disruption with the receptors results in neurophysiological symptoms like learning

and memory impairment. EAA are needed for the memory and brain plasticity and activated NMDA or high exposure to NMDA may disrupt the plasticity of brain (9).

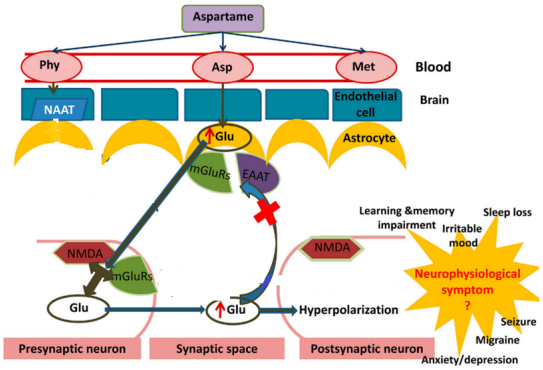

Figure 7. Which Receptors Aspartic Acid Acts Upon (Choudry, 2017)

As the plasticity of the brains is disrupted, the hippocampus area of the brain is effected which is responsible for memory. Memory loss is a hallmark of AD.

Aspartic Acid - Oxidative Stress Inducer

Long, continuous ingestion of aspartic acid is said to induce oxidative stress. Not only aspartic acid metabolite of aspartame, but even methanol is said to induce oxidative stress (17). In another study, aspartic acid was given at different doses to the rats, and the oxidative markers were tested after rats exposure to aspartic acid. Levels of malondial aldehyde (MDA), reactive oxygen species (ROS) and hydroperoxide (H_2O_2) were measured to assess the oxidative stress levels. The following figure 8 was made by Muralidhara, to illustrate that as the aspartic acid amounts were increased from zero to 100 to 500 mg/kg, the amount of hyrdoperoxide formation increased, both in cytosol and mitochondria. It shows an increment in levels of H_2O_2 of 20 to 40%. This indicates the high effect of aspartic acid to oxidative stress (18). In subheading of 2.3 above, it was described how oxidative stress and AD is associated.

The free radicals, H_2O_2 radicals, all together causes oxidative stress and oxidative stress is said to induce neuronal death in AD (19). Thus, as aspartic acid is ingested, it increases the free radicals formation which in return induces neuronal death that is observed in AD patients.

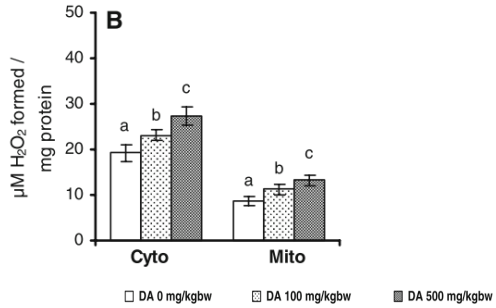

Figure 8. Oxidative Stress Marker Levels Increment (Muralidhara, 2010)

DISCUSSION

Aspartic acid, causes neurotoxicity in brain either by depolarizing that leads of NMDA receptors or by the formation of neurofibral tangles and beta amyloid sheets, or by the neurodegenration due to oxidative stress. All these are related with aspartic acid, because of its excitatory amino acid effect. Aspartic acid play a role in formation of these tangles by, opening up the the Ca^{+2} and causing hyper phosphorylation of tau proteins by activating the phospholipid cascade (9) that is responsible for accumulation of tau proteins, that is known to be one of the two main causes of Alzheimer's disease. (20). Aspartic acid also induces oxidative stress, and oxidative stress in return causes the neurodegenration of hippocampal cells, which results in Alzheimer's disease in long run

REFERENCES

1.Katip I. 'Evaluation of long-term effects of artificial sweeteners on rat brain : A Evaluation of long-term effects of artificial sweeteners on rat brain : a biochemical, behavioral, and histological study'.2018.

2.Richar SS, Hendri HC. 'Diagnosis, Management, and Treatment of Alzheimer Disease', Archives of Internal Medicine, 2003;159(8), p. 789.

3.Alzheimer A. Uber eine eigenartige Erkrankung der Hirnrinde. Allemeine Zeitschr Psychiatr Psy- chisch Gericht Med. 1907;64:146-148.

Received 13.08.2018 Accepted 22.09.2018

4.Niu H. 'Prevalence and incidence of Alzheimer's disease in Europe: A meta-analysis', Neurología (English Edition). Sociedad Española de Neurología, 2017;32(8), pp. 523–532.

5.Khachaturian ZS. Diagnosis of Alzheimer's disease. Arch. Neu- rol. 1985;42:1097-1105;

6.Fallis A. 'Beta-amyloid and the amyloid hypothesis', Journal of Chemical Information and Modeling, 2013;53(9), pp. 1689–1699.

7.Kumar K. 'Recent advances in the neurobiology and neuropharmacology of Alzheimer ' s disease Biomedicine & Pharmacotherapy Recent advances in the neurobiology and neuropharmacology of Alzheimer ' s disease', 2017.

8.Durst F, Tropea C. 'Flows over Two-Dimensional Backward — Facing Steps', Structure of Complex Turbulent Shear Flow, 2011;8(6), pp. 41–52.

9.Haider W, Lackner F, Tonczar L. 'Verabreichung Hochprozentiger Glucose Mit Grossen Insulindosen Im Rahmen Einer Fruhzeitigen Totalen Parenteral Ernahrung Bei Patienten Mit Schockbedingtem Ubersteigerten Kalorienbedarf', Anaesthesist, 1975;24(7), pp. 289–298.

10.Dawkins E, Small, Insights into the physiological function of the β-amyloid precursor protein: beyond Alzheimer's disease, J. Neurochem. 2014;129 (5) 756–769.

11.Johnson E. 'Aspartic Acid', Reference Module in Biomedical Sciences, 2017.

12.Rui W. Role of Glutamate and NMDA Receptors in Alzheimer's Disease.' Journal of Alzheimer's Disease. 2016;57(4) P 1041-1048.

13.Cotman CW, Iversen LL. Excitatory amino acids--focus on NMDA receptors. Trends Neurosci. 1987;10:263-265.

14.Chau V. 'Hypoxic- Ischemic Brain Injury in the Term Newborn' Swaiman's Pediatric Neurology. Ed 6th .2017.

15.Medicine Net. 'Medical Definition of Agonist' [Online] Available from: https://www.medicinenet.com/script/main/art.asp?articlekey=7835

16.Smith CCT, Bowen DM, Francis PT, Snowden JS, Neary D. Putative amino acid transmitters in lumbar cerebrospinal fluid of patients with histologically verified Alzheimer's dementia. J. Neurol. Neurosurg. Psychiatry.1085; 48:469-471.

17.Christian B, Mc-Connaughey K, Bethea E, Brantley S, Coffey A, Hammond L, S. Harrell S et al. Pharmacol. Biochem. Behav. 2004; 78(1), 121.

18.Muralidhara KNCÆ. 'Aspartic acid induced oxidative stress and mitochondrial dysfunctions in testis of prepubertal rats', 2010.pp. 817–827.

19. Simonian NJ. Oxidative stress in neurodegenerative diseases, Annu. Rev. Pharmacol. Toxicol. 36 (1) (1996) 83–106.

20.Rogers J, Morrison JH. Quantitative morphology and regional and laminar distributions of senile plaques in Alzheimer's disease. J. Neurosci. 5:2801-2808: 1985.

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