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Review article

The debate over neurotransmitter interaction in aspartame usage

Arbind Kumar Choudhary [a,b,*], Yeong Yeh Lee [a,1]

[a] School of Medical Sciences, Universiti Sains Malaysia, Kota Bharu, Kelantan, Malaysia
[b] Dept. of Physiology, Government Medical College, Shivpuri, M.P., India

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ABSTRACT

Aspartame (NutraSweet®, Equal®) is a widely used artificial sweetener, has been reported to be accountable for neurological and behavioural disturbances in people. Upon ingestion, aspartame is hydrolyzed in gut and provides its metabolite; such as essential amino acid phenylalanine (Phy) (50%), aspartic acid (40%), and methanol (10%). Altered brain neurochemical compositions [such as dopamine (DA), norepinephrine (NE), and serotonin (5-HT)] have long been a concern and being involved in observed neurophysiological symptom (such as headaches, memory loss, mood changes, as well as depression) in aspartame consumers. Aspartames might act as chemical stressor through increasing plasma cortisol level. Aspartame consumption similarly altered gut microbiota. Taken together all this factors, we reviewed to search for convincing evidence, in what manner aspartame metabolites, stress hormones (cortisol), and gut dysbiosisis involved in altering brain neurochemical composition. We concluded that aspartame metabolite; mainly Phy and its interaction with neurotransmitter and aspartic acid by acting as excitatory neurotransmitter causes this pattern of impairments. Along with elevated cortisol and gut dysbiosis via interactions with different biogenic amine may also have additional impact to modulate neuronal signaling lead to neurobiological impairments. Hence ongoing research is instantly needed to understand the specific roles of aspartame metabolite, elevated cortisol, and gut dysbiosis with emerging neurophysiological symptom in aspartame consumers to improve healthy life in its consumers.

1. Introduction

Aspartame is incorporated into several products including 600 pharmaceutical merchandise [1,2] and is consequently consumed by millions of humans internationally and this may result in oxidative stress by means of affecting a variety of cells and tissues and inflicting a deregulation of cellular function [3]. The dipeptide aspartame, an extensively used artificial sweetener, has been the subject of discussion these days due to its suspected adverse results on the human health consisting of neurologic and behavioral disturbances [4–8].

The products containing aspartame (NutraSweet®, Equal®) had been associated with neuropsychiatric reactions (headache, seizures, depression), and neurologic problems (multiple sclerosis and, Alzheimer's disease) [9,10] as well as with brain tumors [11,12]. Individuals consuming large amounts of aspartame not only may suffer from health consequences but also adverse withdrawal reactions.

Aspartame (L-aspartyl-L-phenylalanine methyl ester) differs from different dietary sweeteners, upon consumption, it is either hydrolyzed or undergo through de-esterification within the body to its essential constituents i.e. amino acid phenylalanine (Phy) (50%), aspartic acid (40%), and methanol (10%) [13]. After absorption, phenylalanine is transformed specifically into tyrosine and to a lesser volume, phenylethylamine and phenylpyruvate. While, aspartic acid is transformed into alanine in addition to oxaloacetate as well as methanol is transformed into formaldehyde and then to formic acid [14,15].

The monoamine neurotransmitters consisting of serotonin (5-hydroxytryptamine, 5-HT), norepinephrine (NE), and dopamine (DA) play an important roles in mood, cognition, learning, motor activity, vigilance, reward, sleep, appetite, and cardiovascular function [16].

The aspartame components can alter brain neurochemical composition and feature an impact on the levels of neurotransmitters within the brain [13]. The behavioral effects may additionally accompanied with alterations in brain neurochemical concentrations after aspartame ingestion [13,17,18]. The frequency of seizures was enhanced using aspartame in doses that elevate plasma phenylalanine levels more than tyrosine, [19,20]. Neurobehavioral

* Corresponding author.
E-mail address: arbindchoudhary111@gmail.com (A.K. Choudhary).
[1] Professor of Medicine, Consultant of Gastroenterology, Hepatology & Internal Medicine, School of Medical Sciences, Universiti Sains Malaysia.

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symptom (such as headaches, memory loss, mood changes, and also depression) was also observed after aspartame usage [5–8]. Altered brain neurochemical levels have long been a concerned due to its terrible effects on neurological function. Studies suggest the role of aspartame in altering brain biogenic amines stays doubtful and those factors may involve in observed neurophysiological symptom. Taken along, we have to search for convincing evidence that, how aspartame and its subsequent increase in metabolite, and stress hormones (e.g., cortisol) as well as gut dysbiosis involved in altering brain neurochemical composition (such as DA, NE, 5-HT) and its consequences.

2. Aspartame metabolites and biogenic amine

The large neutral aminoacid (LNAA) carrier system is composed of amino acid transporters for neurotransmitter synthesis specifically with inside the brain [21] and competes for a similar binding site with in the brain-[22]. The aminoacids, phenylalanine (Phy), tyrosine (Try), and tryptophan (Trp), depend on this carrier system for entry into the brain to help the synthesis of neurotransmitters inclusive of NE, DA, and 5-HT. And any alterations with in these precursors would possibly have the capability to affect neurotransmitter concentrations within the brain.

Table 1
Inconsistent effects of aspartame on neurotransmitter (dopamine, catecholamine and serotonin) levels after administration in animals (no human studies).

S. no	Study design	Results	Conclusion	References
1	The administration by gavage of aspartame (50, 100 mg/kg 200 mg/kg) in adult rats.	After 60 min, there were considerable increments in blood and brain levels of phenylalanine and tyrosine but did not reduce brain tryptophan levels. Moreover there were insignificant increases in dopamine, norepinephrine and serotonin levels.	Aspartame causes large increments in brain phenylalanine and tyrosine however produces minimal effects on the formation of monoamine neurotransmitters.	[34]
2	Sprague-Dawley (SD)] rats received the aspartame (200 mg/kg) by gavage or parenterallyafter a brief (2-h) fast.	Two hours later, regional brain norepinephrine and its metabolite levels were higher, compared with those of saline-treated control rats.	Aspartame produces higher plasma phenylalanine: tyrosine ratio in different regions of the brain.	[35]
3	Unfasted male CD-1 mice were dosed orally with 13, 130, or 650 mg/kg of aspartame once every three hours.	Significant increases of dopamine, catecholamine and its metabolites were seen in various brain regions, whereas, the serotonin and its metabolites were unaffected by way of aspartame.	Aspartame induces increases in the brain catecholamine precursor, amino acids phenylalanine and tyrosine.	[17]
4	Repeated daily oral doses of aspartame (13, 133 or 650 mg/kg) were given for 30 days to male CD-1 mice.	Increases in adrenergic chemicals were observed shortly after a single exposure but were not apparent after repeated dosing. In contrast, concentrations of serotonin and its metabolites were decreased in several brain regions.	An increased supply of phenylalanine from aspartame may be responsible for the decrease in tryptophan uptake or tryptophan conversion to serotonin.	[18]
5	Both acute and chronic dosages of aspartame were given toovernight fasted rats which were allowed to consume meals with or without protein for two hours.	Acute aspartame ingestion increased both plasma and brain phenylalanine and tyrosine levels, but brain tryptophan levels were not altered while chronic ingestion had no effects on its.	Chronic ingestion of abuse doses of aspartame produces no significant chemical changes in the brain monoamines regardless of dietary protein ingestion.	[36]
6	Aspartame and its metabolite, phenylalanine was given orally at doses of 1000 and 500 mg/kg, respectively to rats.	Significant increases were seen in brain phenylalanine and tyrosine levels but no modifications were found in concentrations of monoamines or their metabolites in striatum, hippocampus and nucleus accumbens.	Aspartame does not modify basal brain levels of DA, 5-HT or their metabolites.	[37]
7	Two doses (250 and 1000 mg/kg body weight) of aspartame were administered orally to male rats.	In both plasma and brain the maximum increases in phenylalanine and tyrosine levels were reached 60 min after treatment. However, no significant modifications of monoamine levels were found at any of the time points studied of as much as 5 h after dosing.	No detectable changes in brain monoamine levels	[38]
8	Regional brain concentrations of biogenic amine were evaluated, at 30, 60, 120, or 240 min after oral aspartame (1000 mg/kg) administration in the brain regions of Fischer and Sprague-Dawley rats.	Aspartame in Fischer or Sprague-Dawley rats had no significant effects on levels of the catecholamines or indoleamines at any of the time points monitored.	Large oral loads of aspartame do not appear to lead to regional alterations in brain biogenic amine levels.	[39]
9	Oral administration of acute (50–2000 mg/kg) or sub-chronic (up to 863 mg/kg/day for 28 days) doses of aspartame to genetically epilepsy-prone rats (GEPRs)	Aspartame dosage did not alter seizure severity in either of two types of GEPRs, however produced dramatic changes in plasma and brain amino acid concentrations. At the same time, as alterations in monoamine neurotransmitter systems had been largely absent.	Aspartame does not facilitate seizures in GEPRs as well as not alters the level of brain monoamine levels.	[40]
10	Long-Evans rats received aspartame (200–800 mg/kg, i.p)	Aspartame significantly increased striatal levels of serotonin.	High doses of aspartame reduceaggressive attack of rats via a serotonergic mechanism while the lower dose is without effect on either variables.	[41]
11	Extracellular dopamine levels in the striatum of rats were measured to assess aspartame effects.	A significant decline in dopamine levels within 1 h of a single systemic dose (500 mg/kg;i.p.) when compared to controls.	Aspartame has a relatively potent effect of decreasing evoked extracellular dopamine levels.	[25]
12.	Aspartame (0.625–45 mg/kg) was given via subcutaneous route to evaluate oxidative stress and brain monoamines after intraperitoneal (i.p.) administration of lipopolysaccharide (LPS;100 μg/kg) in mice	Aspartame alone caused dose-dependent inhibition of brain serotonin, noradrenaline, and dopamine and with the administration of LPS increased caused marked increase in brain monoamines.	Aspartame alone or in the presence of mild systemic inflammatory response increases oxidative stress and inflammation in the brain.	[42]

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