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Systematic Review

Aspartame and the brain: a systematic review of neurological effects

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ABSTRACT

Artificial sweeteners like Aspartame are popular due to their low caloric value. They are used as a substitute for sugar, especially for individuals with diabetes and obesity. However, its effects on the neurological system have been debated. Studies suggest aspartame metabolism can lead to altered neurotransmitter synthesis. This review aims to gather literature on the neurotoxic effects of aspartame in humans, aiming to curb this problem. The review was conducted using PubMed, Europe PMC, Cochrane, and Google Scholar. The quality and risk of bias of the extracted studies were assessed using the Critical Appraisal Skills Programme (CASP) checklist, specifically designed for Randomized Controlled Trials (RCTs). The systematic review of aspartame consumption was conducted using PRISMA guidelines and included 11 articles. The studies investigated the effects of aspartame consumption on behavior, cognition, and neurological function through RCTs of varying durations and across different age groups. Aspartame was the primary intervention in all studies, with some neuro biomarkers assessed mainly phenylalanine and tyrosine levels. While some studies reported negative impacts on the above-mentioned parameters others found no significant adverse effects. The review of studies on the effects of aspartame consumption on behavior, cognition, and neurological function reveals mixed results. Neurobiomarkers, specifically phenylalanine and tyrosine, were not consistently assessed across all investigations, making it difficult to establish a clear link between aspartame consumption and neurobiological changes. The studies reviewed provide valuable insights into aspartame effects but highlight complexity. Further research is needed to address limitations.

Keywords: Aspartame, Artificial sweetener, Neurodegeneration, Neurotoxicity

INTRODUCTION

Artificial sweeteners have been globally popular since their introduction, owing to their low caloric value despite retaining sweetening properties. Some marketed examples include Aspartame, sucralose, neotame, and many others, also known as non-nutritional sweeteners (NNS) or non-caloric sweeteners.[1] Therefore, nowadays they are being used as a substitute for sugar, especially for patients with DM and obesity, hence aiding in low caloric intake, weight loss, and preventing dental caries.[1,2] Aspartame is one of the widely used NNS from beverages to drugs. It is a compound of L-aspartic acid with L-phenylalanine methyl ester, discovered in 1965 and around 200 times sweeter than sucrose.3 The acceptable daily intake (ADI) of aspartame as per the US FDA is 50 mg/kg/day and as per WHO (2004) is 40 mg/kg/day.[1] The effects of aspartame on the neurological system, including cognition and behavior, have been debated since its advent.[4] One of the studies suggested that the methanol produced during the metabolism of aspartame induces cytotoxic effects on human cells through a multifactorial pathway. Many experiments with animal models pointed towards the role of aspartame in

the malignant transformation of cells.[5] Moreover, evidence of altered neurotransmitter synthesis and ionic homeostasis has been postulated in some animal studies.[6] When metabolized, APM produces phenylalanine, aspartame acid and methanol. Both amino acids act as precursors and neurotransmitters, respectively in CNS and are reported to decrease dopamine levels in the stratum whereas methanol has an oxidative effect that could be possibly responsible for affecting neurocircuit, thereby producing various neurological and behavioral symptoms such as convulsions, altered mood and cognition, depression, and migraine.[5-7] However, limited studies shed light on the neurotoxicity effects of aspartame in humans and many more gives controversial evidence for the same. This review helps in assembling available literature on the neurotoxic effects of aspartame in humans so that appropriate measures are taken to curb this problem. The popularity of aspartame is rising in the young as well as the older populations, not only as a replacement for sugar for DM and obese patients but also as a food additive amongst youngsters in this health-cautious era.

Research question

What is the impact of aspartame consumption on cognitive function, neurodevelopment, and the risk of neurodegenerative diseases in individuals of all ages?

METHODS

Protocol and registration

This systematic review was registered on Prospero.

Eligibility criteria

Studies were included based on the following inclusion criteria: Individuals of all ages who had consumed aspartame, Consumption of products containing aspartame (e.g., beverages, foods, sweeteners). Studies with one or more of the following comparison groups such as Placebo or control groups, Different levels of aspartame consumption, No consumption of aspartame. Studies with one of the following outcomes: the effect on cognitive function, neurodevelopment, and neurodegenerative diseases were included. Studies had to be published in English. Studies published until January 2024. Studies should have been accessible as open access. Only human studies were included. Case reports, narrative reviews, and editorials were excluded as they did not meet the criteria for systematic evaluation.

Information sources

Searches were performed electronically on applications such as PubMed, Europe PMC, Cochrane and Google Scholar from the database inception to January 2024.

Search

A comprehensive search strategy was employed using the following keywords, Boolean operators, truncation, and MeSH terms ("aspartame" or "L-aspartyl-L-phenylalanine methyl ester") and ("neurological effects" or "cognitive function" or "neurodevelopment" or"neurodegenerative diseases").

Study selection

The study selection process was done by RK, RD, S using the Rayyan platform to manage and screen articles for inclusion in this systematic review.

Data collection process

Data from the included studies were systematically extracted to ensure accurate and comprehensive information retrieval. To facilitate this process, a structured spreadsheet was created to organize the relevant data points.

Addressing data discrepancies

Data extraction was conducted by RK, RD, and S. In cases where discrepancies or disagreements arose during the data extraction process, a collaborative approach was adopted for resolution. Disputes were resolved through mutual discussion and deliberation among the involved researchers. This collaborative discussion allowed for a comprehensive evaluation of the conflicting data points, and a final decision was reached by RK to ensure the accuracy and consistency of the extracted data. This meticulous approach to data extraction and dispute resolution aimed to enhance the reliability and validity of the systematic review's findings by minimizing potential errors or inconsistencies in the extracted information.

Data items

The extracted data included the key characteristics including the age of the participants, study design and duration, sample size (varied from 10-48 in the included studies), the nature and form of aspartame consumption, amount of aspartame consumed, description of the control group and the outcome measures. The main outcome of interest was neurotoxic effects. The data also focused on the duration of exposure and the neurotoxic effects, any reported changes in biomarkers, the proposed mechanisms of action, methods for assessing neurotoxicity, the limitations of the studies and the potential confounding factors not addressed.

Risk of bias in individual studies

Assessment of quality and risk of bias

In the systematic review, the quality and risk of bias in the included studies were assessed using the Critical

Appraisal Skills Programme (CASP) checklist, specifically designed for Randomized Controlled Trials (RCTs). This checklist provides a structured framework for evaluating the methodological quality and potential biases in RCTs.

Process

The assessment of quality and risk of bias was conducted collaboratively by RK, RD, and S, ensuring a thorough evaluation. The process involved the steps:

Checklist application

The CASP checklist for RCTs was applied to each included study. This checklist covers key aspects related to the design, conduct, and reporting of RCTs, including randomization, allocation concealment, blinding, and outcome assessment.

Table 1: The questions answered in the study.

Did the trial address a clearly focused issue?
Was the assignment of patients to treatments randomized?
Were patients, health workers, and study personnel blinded?
Were the groups similar at the start of the trial?
Aside from the experimental intervention, were the groups treated equally?
Were all the patients who entered the trial properly accounted for at its conclusion?
How large was the treatment effect?
How precise was the estimate of the treatment effect?
Can the results be applied in your context (or to the local population)?
Were all clinically important outcomes considered?
Are the benefits worth the harms and costs?

Individual assessment

Each researcher independently assessed the quality and risk of bias in the included studies based on the CASP checklist. This individual assessment allowed for an initial evaluation of the studies.

Discussion and consensus

Following the individual assessments, RK, RD, and S engaged in discussions to compare their evaluations and resolve any discrepancies or disagreements. This collaborative approach ensured a comprehensive evaluation and addressed potential biases.

Final decision

Ultimately, a final decision regarding the quality and risk of bias in each study was reached through consensus. This final decision was based on the collective assessment of the research team. By employing the CASP checklist and conducting a collaborative evaluation, the systematic review aimed to provide a rigorous assessment of the quality and potential biases in the included RCTs. This process contributed to the overall validity and reliability of the systematic review's findings and conclusions.

Results of synthesis

In this systematic review, data synthesis primarily involved a narrative synthesis approach due to the nature of the included studies. Here's an overview of how the data were synthesized:

Study characteristics

The study characteristics extracted from each included study, such as study design, sample size, intervention details, and outcomes, were summarized in a narrative format. This allowed for a comprehensive overview of the included studies.

Quality assessment

The results of the quality assessment, including the assessment of risk of bias using the CASP checklist for RCTs, were summarized for each study. Any potential biases or limitations identified in the studies were discussed in the narrative synthesis.

Findings and outcomes

The findings and outcomes of each study were presented in a narrative manner. This included a description of the observed effects of aspartame on cognitive function, neurodevelopment, and neurodegenerative diseases, as well as any reported changes in Neurobiomarkers.

Proposed mechanisms and limitations

Proposed mechanisms of action and study limitations were also discussed in the narrative synthesis, providing context for the interpretation of study results.

While quantitative analysis (meta-analysis) was not conducted in this systematic review, the narrative synthesis allowed for a comprehensive and qualitative summary of the included studies. This approach provided insights into the effects of aspartame on the outcomes of interest and considered the quality and potential biases of the included studies.

RESULTS

The systematic review was conducted according to PRISMA guidelines and the protocol was registered on Prospero with registration number CRD42023460391.

Study selection

Screening for eligible studies was conducted using the Rayyan platform by RK, RD, and S. During this process, records were assessed against the predefined inclusion and exclusion criteria to determine their suitability for inclusion in the systematic review. Duplicates were identified and removed prior to screening to ensure that each unique record was considered. In total, 369 records were screened, and 15 reports were sought for retrieval. Subsequently, reports that did not meet the eligibility criteria were excluded, including those published prior to 1983 (3 reports) and studies that did not align with the specified population and outcome (7 reports). Finally, 11 articles were included for conducting a systematic review, the process of which is described in Figure 1. This process ensured the systematic selection of studies that met the criteria for the systematic review.

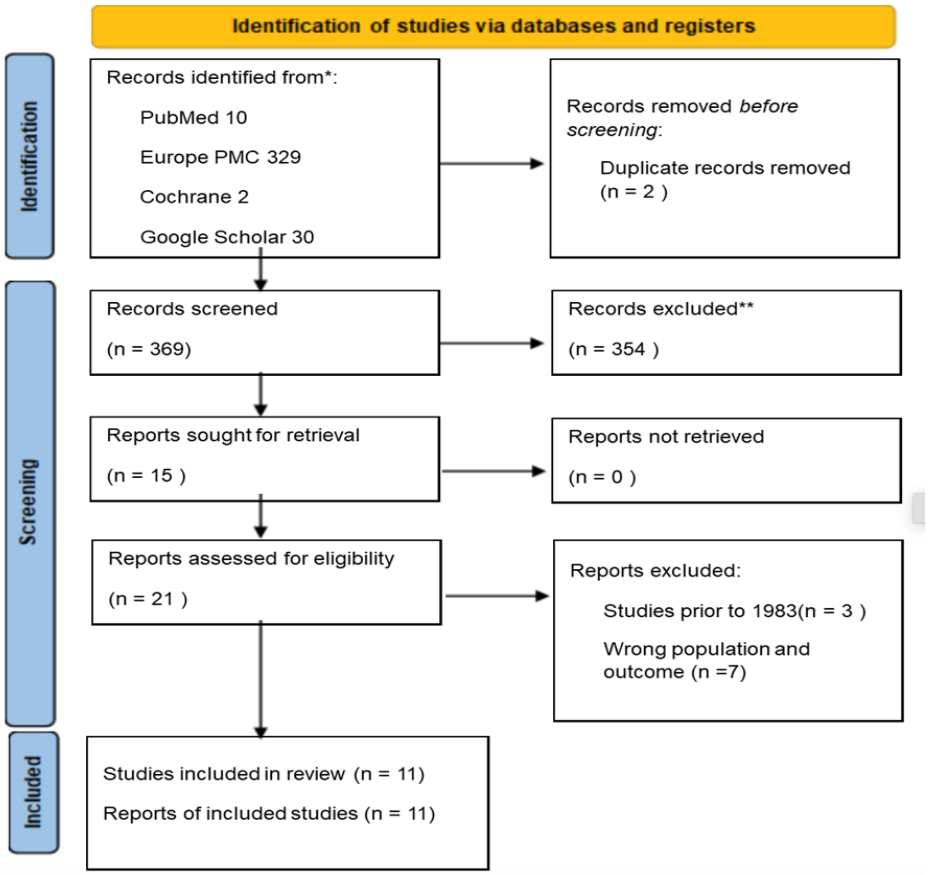

Figure 1: PRISMA flowchart of study selection.

Characteristics of included studies

The characteristics of included studies are summarized in Table 2.

In these diverse studies conducted between 1990 and 2018, the effects of aspartame consumption on behavior, cognitive performance, and neurological function have been investigated through randomized controlled trials (RCTs) of varying durations and across different age groups. Sample sizes ranged from as few as 10 participants to as many as 48, with study durations spanning from a single day to 912 days. The age of participants varied from 3 to 40 years, encompassing children, adults, and specific populations such as individuals with attention deficit disorder, documented seizures, or phenylketonuria. Aspartame was the primary intervention in all studies, administered at different doses, with some investigations assessing neuro biomarkers like phenylalanine and tyrosine levels and triglycerides. While certain studies reported negative impacts on cognitive performance, memory, and behavior, others found no significant adverse effects. These divergent findings highlight the complexity of assessing the impact of aspartame on neurological and cognitive functions and emphasize the need for further research to understand its effects comprehensively.

Risk of bias within studies

The results of the quality assessment for each included study are presented in Table 3.

Table 2: Characteristics of included studies.

First Author	year	Sample size	Age	Population	Intervention	Neurotoxic effect	Duration of exposure and neurotoxic effects (days)	Neurobiomarkers change
Wolraich et al[8]	1994	25	Child	Healthy	Aspartame	Cognitive Performance	7	NA
Wolraich et al[8]	1994	23	Child	Sensitive to Sugar	Aspartame	NA	7	NA
Spiers et al[9]	1998	48	Adult	Healthy	Aspartame	NA	20	Phenylalanine
Lindseth et al[10]	2014	28	Adult	Healthy	Aspartame	Psychological, Orientation, Memory	8	NA
Crézé et al[11]	2018	18	NA	Healthy	NNS	Brain Response	1	NA
Shaywitz et al[12]	1994	10	Child	Seizure Disorder	Aspartame	NA	14	Phenylalanine and Tyrosine
Shaywitz et al[13]	1994	NA	NA	ADHD	Aspartame	NA	14	Phenylalanine and Tyrosine
Lapierre et al[14]	1990	10	Adult	Healthy	Aspartame	NA	NA	Phenylalanine
Trefz et al[15]	1994	48	NA	Heterozygous for phenylketonuria	Aspartame	NA	84	Phenylalanine
Saravis et al[16]	1990	20	Child	Healthy	Aspartame	NA	NA	NA
Saravis et al[16]	1990	20	Child	Healthy	Aspartame	Motor Performance	NA	NA
T. Sathyapalan et al[17]	2015	48	Adult	Sensitive to Sugar	Aspartame	NA	NA	Triglycerides
P. Karstaedt et al[18]	1993	18	Adult	Parkinson's Disease	Aspartame	NA	NA	Phenylalanine

Table 3: Risk of bias assessment.

First Author	Question 1	Question 2	Question 3	Question 4	Question 5	Question 6	Question 7	Question 8	Question 9	Question 10	Question 11	Total
Wolraich et al[8]	2	2	2	2	2	2	2	1	0	2	2	19
Spiers et al[9]	2	2	2	2	2	2	2	2	0	2	2	20
Lindseth et al[10]	2	2	2	2	2	2	2	2	2	2	2	22
Crézé et al[11]	2	2	2	2	2	2	2	2	2	2	2	22
Shaywitz et al[12]	2	2	2	1	2	1	2	2	1	2	2	19
Shaywitz et al[13]	2	2	2	1	2	1	2	0	2	2	2	18
Lapierre et al[14]	2	2	2	2	2	1	2	2	0	2	2	19
Trefz et al[15]	2	2	2	2	2	1	2	1	1	2	2	19
Saravis et al[16]	2	2	2	2	2	1	1	1	1	2	2	18
Sathyapalan et al[17]	2	2	2	1	2	1	2	1	2	2	2	18
Karstaedt et al[18]	2	2	2	1	2	1	2	2	0	2	2	18

Questions were answered from CASP checklist: Did the trial address a clearly focused issue? Was the assignment of patients to treatments randomized? Were patients, health workers, and study personnel blinded? Were the groups similar at the start of the trial? Aside from the experimental intervention, were the groups treated equally? Were all of the patients who entered the trial properly accounted for at its conclusion? How large was the treatment effect? How precise was the estimate of the treatment effect? Can the results be applied in your context (or to the local population)? Were all clinically important outcomes considered? Are the benefits worth the harms and costs?

The numbers indicate:0 indicates no, 1 indicates maybe, 2 indicates yes.

Results of individual studies

Included studies

Authors identified 11 relevant studies that investigated the neurological effects of aspartame consumption. The studies varied in terms of study design, duration, sample size, and age groups. A summary of the key findings from these studies is presented below: In the 1994 study titled "Effects of diets high in sucrose or aspartame on the behavior and cognitive performance of children," 8 conducted by Wolraich et al the researchers employed a randomized controlled trial (RCT) design with a study duration of 21 days. The study comprised a total of 48 participants aged 3 to 10 years, with 25 in the normal population and 23 in the diseased population (specifically, those sensitive to sugar and diagnosed with ADHD/ODD). The intervention involved the administration of aspartame at varying dosages, with the first group receiving 38±13 mg of aspartame per kilogram per day and the second group receiving 32±8.9 mg per kilogram per day with the duration of exposure being 7 days. The control group's diet was high in sucrose with no artificial sweeteners, while the intervention group's diet was low in sucrose and contained saccharin as a placebo sweetener. The primary outcomes assessed were behavior and cognitive performance, with a particular focus on neurotoxic effects. The methods employed for assessing neurotoxicity included the Diagnostic Interview Schedule for Children - Parent Version, Wechsler Intelligence Scale for Children - Revised, and the Wechsler Preschool and Primary Scale of Intelligence, among others. The study data did not specify proposed mechanisms underlying the observed effects. Behaviour and Cognitive Performance was assessed and cognitive performance was negatively affected in the former group. However, it's important to note that the subjects in the study had average or above-average intelligence. In the 1998 study titled "Aspartame: neuropsychologic and neurophysiologic evaluation of acute and chronic effects,"conducted by Spiers et al, the researchers employed a randomized controlled trial (RCT) design with a study duration of 120 days.

The study included a total of healthy 48 participants aged 18 to 35 years. The intervention involved the administration of aspartame at a dosage of 45 mg/kg of body weight. The duration of exposure was 20 days. The primary outcomes assessed in this study included cognitive and behavioral functioning, but not reported any negative outcome in those. The methods employed for assessing neurotoxicity included a wide range of measures, including blood pressure, weight, temperature, heart and respiratory rates, glucose, insulin, amino acid tests, toxin screens, routine hematology (hemoglobin and hematocrit), fasting blood chemistry tests, EEG (electroencephalogram), cognitive tests, and POMS (Profile of Mood States) ratings. The study identified that consuming a protein-rich meal before aspartame ingestion diminished elevations in phenylalanine to large neutral amino acids (Phe:LNAA) ratios. This finding suggested that individuals who restrict food intake and then consume an aspartame-containing beverage with a carbohydrate snack might experience higher Phe:LNAA values acutely. In the 2014 study titled "Neurobehavioral effects of aspartame consumption," 10 conducted by Lindseth, Glenda N, Coolahan, Sonya E, Petros, Thomas V, and Lindseth, Paul D, the researchers conducted a randomized controlled trial (RCT) with a study duration of 30 days.

The study included a total of 28 healthy participants aged 20 to 40 years. The intervention involved the consumption of aspartame at a dosage of 25 mg/kg of body weight per day. The control group received a lower dosage of aspartame at 10 mg/kg of body weight per day. The duration of exposure was 8 days. The primary outcomes assessed in this study included mood, depression, spatial orientation tests, and working memory. Notably, the data indicated that spatial orientation scores were better with the low dosage of aspartame, while working memory was impaired with the high dosage. Additionally, participants reported feeling more depressed after consuming the high dosage of aspartame. The methods used for assessing neurotoxicity included various tests and scales, such as the Vandenberg MRT (Mental Rotations Test), Sternberg Item Recognition Test, and Zung's Self-Rating Depression Scale (SDS). The study done by Crézé et al "The Impact of caloric and non-caloric sweeteners on food intake and brain responses to food: a randomized crossover controlled trial in healthy humans" 11 in the year 2018, focused on the impact of sweeteners on brain response among 18 individuals with no specific age group. the study duration was 1 day, during which subjects (healthy population) were given nns of 70 ml and control (healthy individuals) were given water and sucrose. the outcome of the trial was measured by brain responses to visual food cues using eeg and resulted in a lack of activation of the insula. however, the shorter study duration, absence of neurobiomarkers, and the proposed mechanism for the response have been a major limitation along with the unavailability of any confounding factors.

A randomized controlled trial conducted in 1994, by shaywitz et al on the topic, "aspartame has no effect on seizures or epileptiform discharges in epileptic children" 12, for a period of 4 weeks with the objective of effect of aspartame in diagnosed cases of seizures in children. the study was conducted among 10 children of 5-13 years of age, all confirmed cases of seizures by giving aspartame of 34 mg/kg and measuring the electrical activity by eeg. no significant changes were observed in the eeg of the children after aspartame consumption along with parents' stess and conners ratings. However, increased levels of phenylalanine and tyrosine were found in blood and urine.

The study "Aspartame, behavior, and cognitive function in children with attention deficit disorder" 13, by Shaywitz et al performed in 1994, aimed at the changes in behaviour and cognition of ADHD children upon aspartame consumption. The study period of 2 weeks included the unmedicated children meeting the Diagnostic and Statistical Manual of Mental Disorders (3rd ed) criteria for attention deficit disorder. The intervention was given in the form of aspartame 34 mg/kg or placebo and behaviour and cognitive function was tested using various batteries of tests namely, STESS, MIT, Conners ratings, MFFT, CCT, WCST, Airplane cognition tests, biochemical measures. Apart from increased phenylalanine and tyrosine levels, all tests were unchanged.

In 1990, the study conducted by Lapierre et al titled, "The neuropsychiatric effects of aspartame in normal volunteers" 14, for 1 day period in 10 healthy individuals of the 21-36 years age group. Aspartame, 15 mg/kg, was given and sedation, hunger, headache, reaction time, cognition, or memory were measured with no significant impact on the same because of aspartame. However, such a short study period and small sample size make it difficult to extrapolate the findings on the larger population. In the study titled "Neuropsychological and biochemical investigations in heterozygotes for phenylketonuria during ingestion of high-dose aspartame" by Trefz F and de Sonneville L and Matthis P and Benninger C and Lanz-Englert B and Bickel H conducted in 1994 15, a randomized controlled trial (RCT) with a duration of 84 days and 48 participants, high-dose aspartame ingestion at 45mg/kg/day by heterozygotes for phenylketonuria did not result in any discernible neurotoxic effects on cognitive function. The 84-day exposure led to reported changes in phenylalanine levels, with assessments conducted using EEG and urinary organic acid concentration.

The article "Aspartame: effects on learning, behavior, and mood," by S. Saravis, R. Schachar, S. Zlotkin, Lawrence A Leiter, G. Anderson from 1990 16, reported results of an RCT conducted over 20 days with 20 participants aged 9-10 years. It examined the effects of aspartame at doses of 34 mg/kg and 9.7 mg/kg. The study did not find any significant impacts on learning, behavior, mood, minor and gross motor behaviour . Any observed changes were attributed to the absence of metabolic consequences rather than aspartame's amino acid composition or neurochemical impact.

In 2015, "aspartame sensitivity? a double-blind randomized crossover study" conducted by T. Sathyapalan, N. Thatcher, R. Hammersley, A. Rigby, A. Pechlivanis, N. Gooderham, E. Holmes, C. le Roux, S. Atkin, F. Courts 17, is a comprehensive RCT over 912 days with 48 participants who were sensitive to aspartame. They consumed 100 mg of aspartame. The study assessed psychological conditions, symptoms, biochemistry, and metabonomics using the Beck Depression Inventory (BDI); Hospital Anxiety and Depression Scale (HADS); Perceived Stress Severity Scale (PSS); life events in the past 12 months (SRRI); Toronto Alex-ithymia Scale (TAS-20); Whiteley-7 Somatisation Index; State Trait Anxiety Inventory (STAI), Plasma glucose, lipid profile, Serum CRP, Incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). It also reported an increase in triglyceride levels. It found that the acute effects of aspartame did not lead to significant changes in the parameters measured. However, the study noted the possibility of chronic, cumulative effects of aspartame on biological parameters and psychological state Lastly, "Aspartame use in Parkinson's disease," conducted by P. Karstaedt, J. Pincus in 1993 (18), involved an RCT with 18 participants aged 45-70 diagnosed with Parkinson's disease. The study administered aspartame at doses of 600 mg and 1200 mg. It assessed motor performance and various plasma levels using NYU disability scores, AIMS dyskinesia scores, walking times, plasma large neutral amino acid levels, or plasma levodopa levels, plasma phenylalanine. It reported an increase in levels of phenylalanine and no significant effects on motor performance.

Results of synthesis

We conducted a narrative synthesis of the findings from the studies included the studies included in this analysis investigated the effects of aspartame consumption on various aspects of behavior, cognitive performance, and neurological function across different populations and durations.

Effects on children's behavior and cognitive performance

Two studies on young children found that aspartame consumption negatively impacted cognitive performance in both groups. The duration of exposure was 7 days in each study, and negative effects were observed. However, potential confounding factors were not addressed comprehensively.

Neurobehavioral effects in adults

In a study involving adults, aspartame consumption at 25 mg/kg body weight/day over 30 days had negative effects on psychological, orientation, and memory outcomes.

Impact on brain responses in healthy humans

This study explored the impact of non-caloric sweeteners (NNS), including aspartame, on brain responses within a single day in healthy humans. It reported a negative impact on brain responses.

Effect on epileptic children

In children with documented seizures, aspartame consumption over 28 days did not have a significant effect on seizures. Neurobiomarkers, specifically phenylalanine and tyrosine, were assessed.

Children with attention deficit disorder

In children with ADHD, aspartame consumption over 14 days did not report negative impacts on behavior or cognitive performance. Neurobiomarkers (phenylalanine and tyrosine) were assessed.

Effects on normal volunteers

Among normal volunteers, a short-term exposure of 1 day to aspartame did not report negative impacts on cognitive performance or memory. Phenylalanine was assessed as a neuro biomarker.

Investigation in phenylketonuria heterozygotes

In individuals heterozygous for phenylketonuria, high-dose aspartame consumption over 84 days did not report negative impacts on cognitive performance. The neural biomarker phenylalanine was assessed.

Learning, behavior, and mood

A study explored the effects of aspartame on learning, behavior, and mood. It did not report negative impacts on behavior, psychological, or memory outcomes. Neurobiomarkers (phenylalanine and tyrosine) were assessed.

Aspartame sensitivity

A long-term study over 912 days investigated aspartame sensitivity in individuals sensitive to aspartame. It did not report changes in neuro biomarkers but assessed triglycerides.

Aspartame use in Parkinson's disease

Aspartame use in Parkinson's disease was investigated, although specific study duration details were not provided. Neurobiomarker phenylalanine was assessed at different doses.

Neuropsychologic and neurophysiologic evaluation

In a study spanning 120 days, aspartame consumption did not report negative impacts on behavior or cognitive performance. Neurobiomarker phenylalanine was assessed over 20 days.

Overall, findings varied across these studies, with some reporting negative impacts on cognitive and psychological outcomes, while others did not find significant effects. Neurobiomarkers were inconsistently assessed, and potential confounding factors were not consistently addressed, highlighting the complexity of understanding the impact of aspartame on neurological and cognitive functions. Further research is needed to provide a more comprehensive and conclusive assessment of these effects.

DISCUSSION

The findings from the synthesized studies on the effects of aspartame consumption on behavior, cognitive performance, and neurological function are multifaceted, highlighting both areas of concern and limitations within the research. This finding aligns with previous research that has raised concerns about the safety of aspartame, particularly regarding its neurological impacts. The acceptable daily intake of aspartame for humans is 40 mg/kg bodyweight in Europe and 50 mg/kg bodyweight in the United States for both adults and children according to FDA.[19] It becomes likely that both children and adults can unintentionally consume larger amounts than those recommended by the FDA, which may lead to serious health complications. Previous researches suggest that aspartame and its metabolites increase the risk of neurodegenerative diseases such as Alzheimer’s disease, Parkinsonism, multiple sclerosis, and brain tumors.[20] Here, we discuss these findings and their broader implications for the field, while also addressing the limitations of this review and the included studies:

Mixed effects on cognitive and psychological outcomes

The studies presented a mixed picture of the impact of aspartame on cognitive and psychological outcomes. Some studies reported negative effects, particularly on cognitive performance and psychological well-being, while others did not find significant adverse impacts. [8,10] This variability suggests that individual responses to aspartame may differ, and factors such as age, sensitivity, and pre-existing conditions might play a role in these outcomes.

Limited assessment of neurobiomarkers

Neurobiomarkers, specifically phenylalanine and tyrosine, were assessed in some studies, but not

consistently across all investigations. 9,12-15 The lack of comprehensive assessment makes it challenging to establish a clear link between aspartame consumption and neurobiological changes. More studies that delve into the biochemical aspects of aspartame metabolism are needed to better understand its effects on neurobiological processes.

Duration of exposure matters

The duration of exposure to aspartame varied widely among the studies. Some studies assessed short-term effects over a few days, while others conducted long-term investigations spanning several months. The duration of exposure might influence the observed outcomes, and future research should consider this factor when designing studies.

Population-specific effects

The impact of aspartame appeared to vary depending on the population studied. For example, studies on children with ADHD or epileptic children did not consistently report negative effects, while studies on normal volunteers or individuals with specific conditions like phenylketonuria yielded different results. 12,13,15,18 This suggests that aspartame's effects might be population-specific and influenced by underlying health conditions.

Unaddressed confounding factors

Many of the studies did not comprehensively address potential confounding factors. This omission makes it challenging to isolate the effects of aspartame accurately. Factors such as diet, genetics, and overall health should be considered in future research to improve the reliability of the findings.

Broader implications

The mixed findings in these studies underscore the need for more robust and well-controlled research on aspartame's effects. Given the widespread use of artificial sweeteners in various food products, understanding their potential impacts on behavior, cognition, and neurobiology is of substantial public health importance. Future research should employ rigorous methodologies, consider individual differences, and assess neurobiological markers to provide clearer insights.

There is no previous systematic review done in this field as per our search. Thus, we can't compare it to any previous systematic reviews.

Limitations

This review is based on the information provided and may not capture all nuances or additional findings from the original studies. Lack of Access to Full Texts: Detailed interpretations and discussions would require access to the full texts of the studies, which are not available in this context.

CONCLUSION

In conclusion, while the studies reviewed here offer valuable insights into the effects of aspartame, they also highlight the complexity of the issue. To draw more definitive conclusions and address the limitations observed, further research that considers individual variability, assesses neurobiological markers comprehensively, and accounts for potential confounding factors is essential. Such research is crucial not only for scientific understanding but also for informing dietary recommendations and public health policies regarding the consumption of artificial sweeteners

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