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ARAŞTIRMA YAZISI / RESEARCH ARTICLE

7,8 DHF, BİR TRKB AGONİSTİ, KAFETERYA DİYETİ TARAFINDAN İNDÜKLENEN KORTİKAL BOZULMAYI İYİLEŞTİRİR

7,8 DHF, A TRKB AGONIST, AMELIORATES CORTICAL IMPAIRMENT INDUCED BY A CAFETERIA DIET

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ÖZET

AMAÇ: Bu çalışmanın amacı, kafeterya diyetinin beyin üzerindeki olumsuz etkileri ile bu diyetin oluşturduğu kortikal bozukluğun iyileştirilmesinde bir tropomiyozin reseptör kinaz B (TrkB) agonisti olan 7,8-Dihidroksiflavon (7,8-DHF) arasındaki ilişkiyi araştırmaktır.

GEREÇ VE YÖNTEM: Çalışma, Karadeniz Teknik Üniversitesi'nden temin edilen 40 C57BL/6 fare ile gerçekleştirildi. Fareler dört gruba (n=9-11) ayrıldı: Kontrol, kafeterya diyet (Caf), çözücü ile birlikte kafeterya diyet (Sham) ve 7,8-Dihidroksiflavon (7,8-DHF) ile kafeterya diyet. Kontrol grubu fareler kontrol diyeti alırken, diğer gruplara 16 hafta boyunca kafeterya diyeti verildi. Son 28 gün boyunca, 7,8-DHF grubuna 5 mg/kg 7,8 DHF uygulanırken, sham grubuna çözücü verildi. Sonra, davranış testleri (silindir testi, telde asılı kalma testi, yapışkan çıkarma testi) yapıldı ve fareler doku örneklemesi için dekapite edildi. Biyokimyasal veriler oksidatif stres analizi için değerlendirildi.

BULGULAR: Yapılan davranış testleri sonucunda, 7,8-DHF grubunun telde asılı kalma testinde Caf gruba göre daha iyi performans gösterdiği kaydedildi. Biyokimyasal analizlerde, 7,8-DHF'nin hem hipokampüs hem de korteks dokularındaki malondialdehit (MDA) seviyelerini önemli ölçüde azalttığı görüldü. Toplam antioksidan seviyeleri, MDA seviyelerindeki azalmayı tamamladı.

SONUÇ: 7,8-DHF, kafeterya diyeti ile indüklenen oksidatif stresi azaltarak kortikal fonksiyonları iyileştirmiştir. Bu çalışma, bu küçük molekülün kafeterya diyeti alışkanlıklarından kaynaklanan olumsuz sonuçlara karşı koruyucu etkiler sağlayabileceğini öne sürmektedir.

ANAHTAR KELİMELER: Kafeterya diyeti, 7,8-DHF, Korteks, Davranış testleri, Oksidatif stres.

ABSTRACT

OBJECTIVE: The aim of this study is to investigate the relationship between cafeteria diet and its negative effects on the brain and the effects of 7,8-Dihydroxyflavone (7,8-DHF), a tr opomyosin receptor kinase B (TrkB) agonist, in ameliorating cortical impairment induced by this diet.

MATERIAL AND METHODS: The study was conducted with 40 C57BL/6 mice obtained from Karadeniz Technical University. The mice were divided into four groups (n=9-11): Control, cafeteria diet (Caf), cafeteria diet with vehicle (Sham), and cafeteria diet with 7,8-Dihydroxyflavone (7,8-DHF). The Control group of mice received a control diet, while the other groups were fed a cafeteria diet for 16 weeks. During the last 28 days, 5 mg/kg of 7,8 DHF was administered to the 7,8-DHF group, while the sham group received a vehicle solution. After the experimental period, behavioral tests (cylinder test, hang wire test, adhesive removal test) were performed and the mice were decapitated for tissue sampling. Biochemical data were evaluated for oxidative stress analysis.

RESULTS: Behavioral test results showed that the 7,8-DHF group performed better in the hang wire test compared to the Caf group. In biochemical analyses, it was observed that 7,8-DHF significantly reduced malondialdehyde (MDA) levels in both the hippocampus and cortex tissues. The total antioxidant levels complemented the reduction in MDA levels.

CONCLUSIONS: 7,8-DHF has ameliorated the cortical functions by reducing oxidative stress induced by the cafeteria diet. This study suggests that this small molecule could provide protective effects against the negative consequences arising from cafeteria diet habits.

KEYWORDS: Cafeteria diet, 7.8-DHF, Cortex, Behavioral tests, Oxidative stress.

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INTRODUCTION

Nutritional chemists have studied complex meal combinations in great detail in order to create "ultra-processed" foods and drinks, which have been implicated as the primary cause of the present obesity crisis worldwide. The unhealthy, overly processed foods that are high in fat and sugar make up the cafeteria diet (1). The cafeteria diet is the closest human counterpart to a diet rich in processed foods (2). Depending on intake, research on both humans and animals indicates that a more varied diet is linked to higher body weight and adiposity (3). Frequent intake of a food high in fat and refined carbohydrates, such as that found at a normal cafeteria, is linked to negative health consequences like obesity, insulin resistance, hyperphagia, and low-grade inflammation associated with obesity. The immune system and ensuing inflammatory state can be changed by high-fat meals because they can activate innate immune cells and cause a brief postprandial inflammatory response (4). Nutritional cues use humoral and vagal systems which have a lot in common with immunological pathways to preserve energy balance. The cafeteria diet results in neurological problems and heightened inflammation. The function of the hippocampus is compromised by a cafeteria diet. In addition to influencing learning and memory function in the hippocampus through synaptic plasticity modulators like brain derived neurotrophic factor (BDNF), these immunological and nutritional signals move systemically to the brain to change hypothalamic-controlled feeding behaviour. Cognitive deficiencies, aberrant immunological responses, and irregular eating patterns are the outcomes of long-term exposure to situations involving excessive calorie consumption (2).

Recent developments in molecular biology have demonstrated that signals originating from food can affect synaptic plasticity and energy metabolism, mediating the effects of food on cognitive performance (5). One neuropeptide plays a neurotrophic effect in physiological processes through its receptor Trk-B is BDNF (6). BDNF is one well-known regulator of synaptic plasticity that can serve as a metabolic modulator in response to external cues like food consumption (7). The acquisition of knowledge and adjustment to novel circumstances are crucial in plasticity. Specific diets can have cumulative impacts on cognitive performance and synaptic plasticity. BDNF may be activated by adenosine triphosphate (ATP) generated by mitochondria. BDNF interacts with energy-balancing molecules to alter synaptic plasticity and cognition. Reactive oxygen species (ROS) are created when the body produces too much energy due to a high calorie intake or intense exercise (8). Acquiring a task enhances BDNF-mediated synaptic plasticity in the hippocampus, while genetic ablation of the BDNF gene hinders memory formation (9). A de novo mutation in TrkB, a receptor for BDNF, has been associated with hyperphagic obesity and deficits in learning and memory in humans. While energy metabolism and BDNF-mediated synaptic plasticity appear to be interrelated, additional research is essential to delineate the parameters of this interaction for cognitive function modulation (10).

7,8-DHF, a small molecule, may imitate BDNF and activate the BDNF/TrkB signalling pathway. It is capable of traversing the blood-brain barrier and has demonstrated the ability to restore various brain functions in experimental models such as aging, Parkinson's disease, and Alzheimer's disease. Research indicates that 7,8-DHF, functioning as a BDNF mimic, may facilitate neurogenesis, improve motor performance, and demonstrate antidepressant properties (11,12). Additionally, 7,8-DHF has been identified as an activator of the TrkB receptor, linked to neuroprotection and synaptic plasticity (13). The prolonged administration of the small chemical 7,8-DHF enhanced age-related deficits in sensorimotor skills (14). The persistent enhancement of TrkB signaling with 7,8-DHF may serve as a viable and successful approach for ameliorating function in Alzheimer's disease, even following significant neuronal degeneration (15). Chronic injection of 7,8-DHF markedly enhanced motor deficits and maintained the number of spinal motor neurons and dendritic spines (16). The current literature indicates that 7,8-DHF may positively affect neurochemical processes, improve motor performance, and offer neuroprotective benefits.

Additional research concentrating on the impact of 7,8-DHF within the framework of a cafeteria diet could provide significant insights into its effectiveness in alleviating the adverse effects associated with such dietary habits. While the impact of the cafeteria diet on the hippocampus is well-documented, the chemical and functional alterations it induces, particularly in the cortex and its modulation by Trk-B agonists remain largely unexplored. This study hypothesizes that the cafeteria diet may adversely affect the cortex, and that such damage could be reduced through BDNF/Trk-B activation. The study presents a novel approach on examining cortical oxidative stress and behavioral outcomes influenced by Trk-B activation.

MATERIALS AND METHODS

Forty male C57BL/6 mice, weighing 10-15g, were procured from the Surgical Practice and Research Centre at Karadeniz Technical University (KTU). The mice were housed and nourished in individually ventilated cage (IVC) systems with 12-hour light/dark cycles. Feed and water were provided ad libitum.

The mice were randomly divided into 4 groups with 10 animals in each group. Group I (Control): Fed chow diet for 16 weeks. Group II (Caf): Fed with cafeteria diet for 16 weeks. Group III (7,8-DHF): fed cafeteria diet for 16 weeks. During the last 28 days of the feeding period, 5mg/kg/day 7,8-DHF was given by intraperitoneal injection (i.p.) (17). Group IV (Sham): Fed a cafeteria diet for 16 weeks. PBS with 17% DMSO was administered via intraperitoneal injection during the final 28 days of the feeding period (13). The cafeteria diet was established as previously outlined by supplementing the chow diet with packaged snack foods, including biscuits, crackers, cakes, chips, and chocolate wafers (18).

At the end of the experimental period, behavior testing was performed. The sensory-motor functions were then tested using the cylinder test, hang wire test, and adhesive removal test. The offline analysis and scoring of the video recordings were verified. The tests were conducted in the animals' natural habitats, with the same researcher engaging with the animals from the outset of the study. For cylinder test, C57BL/6 breed mouse raised to a height of 12 cm (19) in a glass cylinder beaker. For 180 seconds, the number of contact with the glass surface using both forelimbs while standing on its hind legs was tallied. For every mouse, there were three trials and two repetitions.

For hang wire test, a pillow was positioned beneath 35 centimetres, and the mouse was positioned on a stretched, 0.5 cm thick wire. Each mouse's wire-holding duration across a 120-second period was scored four times. . Each mouse underwent two trials with two repetitions For adhesive removal test, red adhesive tape strips, measuring 3 mm by 3 mm, were affixed to the mice's front paws. The rodent has a tendency to detect this unfamiliar item and remove it. The mouse was observed and recorded for three minutes (20) during the moments when it touched the palms and took out the first paper. Then the animals were weighed and sacrificed by decapitation.Hippocampus and cortex tissues were removed and stored at -800C until biochemical analysis.

To measure the parameters determined in the tissue samples, 1.5 mL phosphate-buffered saline (PBS) (pH 7.4) was added to the tissue and homogenized for 20 seconds using a hand homogenizer (IKA, T25 Ultra-Turrax, Staufen, Germany). The homogenate was centrifuged at 3000xg for 15 minutes at 4 °C and biochemical measurements were performed on the supernatants. Protein determination in the supernatants was performed by the Bradford method (21). The results were calculated in mg/mL.

The MDA concentrations in tissue samples were measured using the methodology established by Mihara and Uchiyama (22). This approach relies on measuring the absorbance at 532 nm of the color produced by MDA in conjunction with thiobarbituric acid in an acidic medium. 1,1,3,3-tetramethoxypropane served as a reference, and tissue MDA concentrations were quantified as nmol/g protein. The levels of tissue total oxidant status (TOS) and total antioxidant status (TAS) were assessed utilizing commercial colorimetric kits (Rel Assay Diagnostics, Gaziantep, Turkey) in accordance with the manufacturer's guidelines.

The TOS/TAS ratio served as the oxidative stress index (OSI), calculated using the formula:

OSI (arbitrary unit)= [TOS (μmoL hydrogen peroxide equivalent/L)/ TAS (mmoL trolox equivalent/L)]× 100

Statistical Analiysis

The data are presented as the mean ± standard deviation for ten mice per group in the biochemical and behavioral examination. The conformity of the data to a normal distribution was evaluated using the Kolmogorov-Smirnov test. Group comparisons for biochemical and behavioral data were performed using one-way analysis of variance (ANOVA) followed by Tukey's multiple comparisons test. The data were analyzed utilizing the Statistical Package for the Social Sciences (Version 23.0). The criterion for statistical significance was set at $p < 0.05$.

Ethical Committee

This study was approved by the Animal Care Ethical Committee at KTU with protocol number 2023/44 dated 13/12/23.

RESULTS

There was no significant difference between the groups in the cylinder test (p=0.7617) **(Figure 1)**.

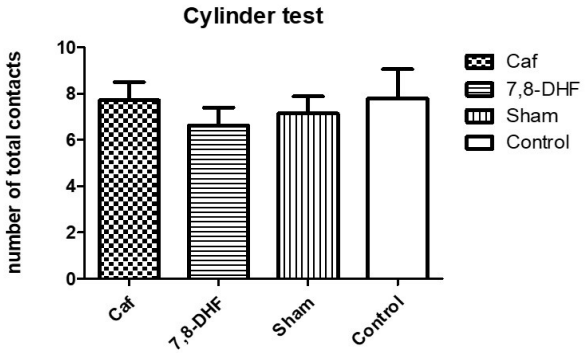


Figure 1: Cylinder test.

The 7,8-DHF group outperformed the Caf group in the hang wire test. **Figure 2** illustrates the mean holding durations in the hang wire test (p=0.4019). According to the adhesive removal test data, the one way ANOVA test showed that there were significant differences across the groups (p <0.05). The adhesive removal first touch test indicated that the 7,8-DHF group exhibited significantly superior performance compared to the Caf and Sham groups (p=0.0070) **(Figure 3)**. Also in the second tape removal test, it was noted that the performance of the Caf group was inferior to that of the Control group (p=0.0284, $p < 0.05$).

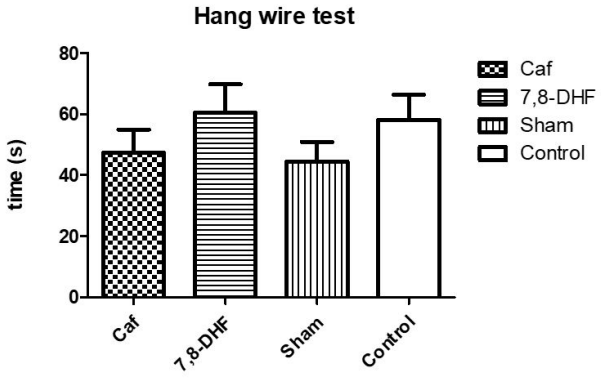


Figure 2: Hang wire test.

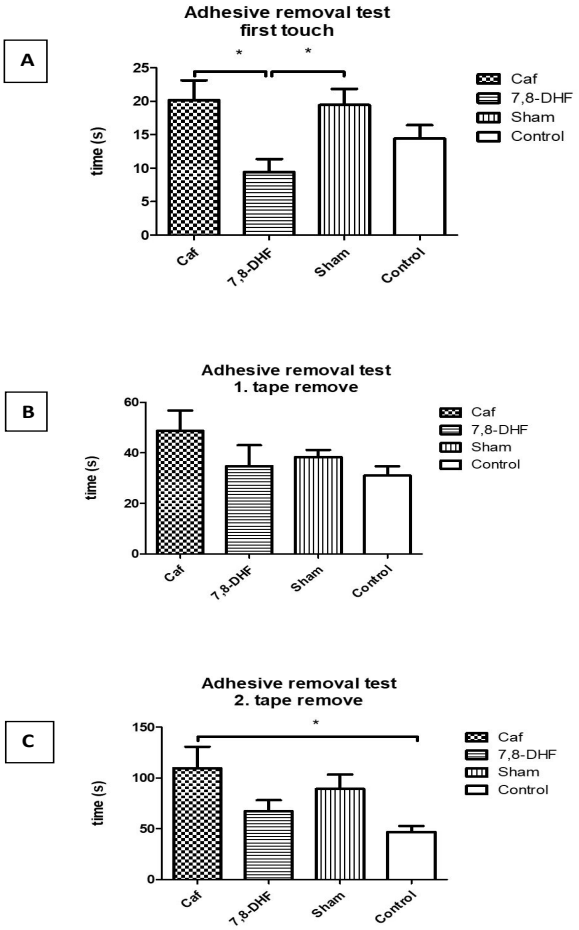


Figure 3: Adhesive removal test
A: Adhesive removal test first touch
B: Adhesive removal test first tape remove
C: Adhesive removal test second tape remove
***:** p<0.05

We examined the impact of 7,8-DHF on oxidative stress induced by a cafeteria diet by asses-

sing MDA, TAS, TOS and OSI levels in the cortex and hippocampus of mouse brains. One-way ANOVA indicated significant differences in MDA levels among the groups in hippocampal tissue. **Table 1** illustrates that the MDA level was significantly elevated in the sham group (22.70±6.41 nmol/g) compared to the control and 7,8-DHF groups (12.67±3.21 nmol/g; 14.06±3.72 nmol/g, respectively) ($p < 0.05$). Additionally, long-term use of 7,8-DHF resulted in a reduction in MDA levels in the 7,8-DHF group relative to the Caf group (20.25±5.21 nmol/g) ($p < 0.05$).

The cortical MDA level in the control group was 10.53±2.08 nmol/g protein, which increased to 30.12±8.31 nmol/g protein in the Caf group ($p < 0.05$). 7,8-DHF (11.88±2.38 nmol/g protein) and sham (16.33±4.99 nmol/g protein) groups exhibited significantly lower MDA levels in cortical tissue compared to the Caf group ($p < 0.05$) (Table 1). There was no significant difference in TAS levels among the groups in either hippocampus (0.55±0.11 mmol trolox Equi/L) and cortex (0.93±0.23 mmol trolox Equi/L) tissues Table 1.

All brain regions' total oxidant status (TOS) values varied significantly between groups. Compared to the 7,8-DHF (12.36±0.83 µmol H_2O_2 Equi/L) group, the sham (13.89±1.12 µmol H_2O_2 Equi/L) group's TOS levels were significantly higher in the hippocampus ($p < 0.05$) (Table 1). The 7,8-DHF (9.68±0.67 µmol H_2O_2 Equi/L) group's levels in the cortex were significantly lower than the Caf (13.68±3.25 µmol H_2O_2 Equi/L) group ($p < 0.05$) (Table 1). OSI values did not significantly differ between groups all tissues.

Table 1: Oxidative Stress Parameters at Hippocampus and Cortex

Hippocampus	**Control**	**Caf**	**7,8-DHF**	**Sham**
MDA (nmol/g protein)	12.67±3.21	20.25±5.21[a]	14.06±3.72[b]	22.70±6.41[a,c]
TOS (µmol H_2O_2 Equi/L)	13.21±1.06	13.56±1.07	12.36±0.83	13.89±1.12[c]
TAS (mmol trolox Equi/L)	0.52±0.05	0.52±0.06	0.55±0.11	0,49±0.13
OSI (arbitrary unit)	2.55±0.37	2.64±0.45	2.30±0.43	3.09±1.28
Cortex	**Control**	**Caf**	**7,8-DHF**	**Sham**
MDA (nmol/g protein)	10.53±2.08	30.12±8.31[a]	11.88±2.38[b]	16.33±4.99[b]
TOS (µmol H_2O_2 Equi/L)	11.79±2.86	13.68±3.25	9.68±0.67[b]	11.91±3.54
TAS (mmol trolox Equi/L)	0.83±0.25	0.88±0.20	0.93±0.23	0.93±0.18
OSI (arbitrary unit)	1.49±0.44	1.66±0.71	1.11±0.33	1.30±0.35

MDA: malondialdehyde, TOS : total oxidant status, TAS : total antioxidant status, OSI: oxidative stress index.
P-values according to one-way ANOVA test, post-hoc Tukey test. Data were expressed as mean ± SD.

[a]$p < 0.05$ compared with Control group.
[b]$p < 0.05$ compared with Caf group.
[c]$p < 0.05$ compared with 7,8-DHF group.

DISCUSSION

Recent studies have increasingly examined the effects of cafeteria diets marked by elevated quantities of fats and sugars on cognitive function and behavior, especially in animal models. Studies demonstrate that cafeteria diets promote hyperphagia (excessive food intake), which is a crucial factor in the development of obesity in both animal models and humans (23). Numerous studies demonstrate substantial neurological alterations correlated with these diets, frequently connected with obesity and metabolic problems. The primary finding indicates that cafeteria diets promote neuroinflammation, especially within the hippocampus, a crucial area for learning and memory processes. Neurogenesis in the dentate gyrus is compromised in adolescent rats consuming a CAF diet, which correlates with heightened anxiety and deficits in spatial learning and memory, characteristics closely associated with the structural integrity of the hippocampus (24). Supporting this, Wait et al. indicated that early postnatal exposure to cafeteria diets disrupts memory processes, especially spatial memory, which is closely associated with hippocampal function (25). Reichelt et al. further showed that the intake of an obesogenic cafeteria meal influences brain areas, including the basolateral amygdala and the orbitofrontal cortex, which are essential for evaluating the incentive value of food and for decision-making based on past experiences (3). The lactational diet that induces obesity has been studied for its detrimental impact on cognitive skills in adolescents children, linked to irregular serotonin and dopamine metabolism in the prefrontal cortex (26). While numerous studies have examined hippocampal function, research on the cortex remains scarce. The impact of cortical dysfunction under cafeteria diet circumstances and its modulation by TrkB agonists has yet to be defined. The research indicated that a prolonged cafeteria diet elevated oxidative stress and lipid peroxidation, which were the principal factors contributing to biochemical decline in the hippocampus and cortex. Cortical functioning was concurrently compromised. The use of 7,8-DHF enhanced behavioral performance and oxidative stress metrics.

This preliminary investigation demonstrates the detrimental effects of a cafeteria diet on the cortex, suggesting that these effects may be partially associated with the BDNF pathway.

Research has extensively examined the neurological impairments linked to cafeteria diets, uncovering notable changes in brain structure, function, and behavior. Cafeteria diets, marked by their elevated caloric density and appealing flavors, have demonstrated a propensity to promote obesity and associated metabolic disturbances, subsequently influencing cognitive abilities and neurochemical processes. Lewis et al. (27) indicated that rats subjected to a cafeteria diet displayed marked impairments in cognitive assessments, including the Morris Water Maze (MWM) and Novel Object Recognition (NOR) tests, suggesting a deterioration in both spatial and non-spatial memory .

A study by Gomez-Smith et al. utilizing a cafeteria diet for three months revealed no significant differences between groups on the Barnes Maze test, which assesses spatial learning and memory (2). Prior research seems to have concentrated on the hippocampus in behavioral tests. Our study focuses on the motor cortex, which has not been previously clarified. Prolonged exposure to a cafeteria diet may predispose individuals to cognitive issues. In our study, mice were administered a cafeteria meal for four months, resulting in a considerable deterioration in performance during motor cortex behavioral studies. The cafeteria diet elevates oxidative stress, but 7-8 DHF treatment alleviates it, with observable consequences on behavior. Biochemical processes associated with oxidative stress can impact behavioral change (28). The inflammatory response within the brain represents a significant element of neurological impairment induced by a cafeteria diet.

Castell-Auví et al. (29) emphasized that extended exposure to cafeteria diets results in insulin resistance and heightened inflammatory markers, which may negatively impact brain health and function. Thompson et al. (30) elucidated that obesity resulting from cafeteria diets leads to modifications in structural and neuronal plasticity within the lateral orbitofrontal cortex (OFC). The research demonstrated that extended exposure to a cafeteria diet results in alterations to the structure of pyramidal cells. Antonio et al. (31) observed that rats consuming a hypercaloric cafeteria diet displayed dyslipidemia, insulin resistance, and heightened oxidative stress, factors that may lead to neuroinflammation and neuronal damage. The association between oxidative stress and disruptions in glucose metabolism, alongside an elevated risk of neurodegenerative disorders, is noteworthy. Our research demonstrated the neurological impairments associated with the cafeteria diet, evidenced by behavioral changes and heightened oxidative stress in the cortical region following exposure to this dietary plan. Our results correspond with those of prior research.

The BDNF/TrkB pathway is crucial for cerebral function, and the cafeteria diet may adversely affect this mechanism. Gutierrez et al. demonstrated in their study that a cafeteria-style diet resulted in increased body fat, poor glucose tolerance, elevated insulin production, enlarged pancreatic islet area, and insulin resistance. Furthermore, the antagonism of the trkB receptor by ANA-12 in cafeteria-fed rats resulted in higher body fat storage, elevated circulating insulin levels, increased insulin resistance, and an expansion of pancreatic islet area. The findings indicate that the trkB receptor plays an essential role in regulating body fat preservation and insulin secretion during long-term use of a cafeteria-style diet (32).

Associated neurochemical alterations in BDNF signaling, notably reduced levels of BDNF and astrocytic markers glial fibrillary acidic protein (GFAP) and peroxisome proliferator-activated receptor gamma (PPARγ) in pertinent brain areas, including the olfactory bulb and hippocampus, have been proposed to correlate with the effects of hypercaloric diet (33). It has been demonstrated that cafeteria diet-induced hyperphagia may result in modifications to the hedonic and motivational regulation of food consumption via abnormalities in dopamine metabolism and BDNF signaling within the nucleus accumbens and dorsal striatum (34).

On the other hand, another study indicated that our continuously limited diet was associated with beneficial effects on BDNF levels and BDNF-TrkB signaling pathway is activated in the prefrontal cortex (35). Concerning the influence of a cafeteria diet on health, few studies have investigated the preventive effects of 7,8-DHF. Research indicates that 7,8-DHF may provide protection against damage caused by obesity and oxidative stress (36). 7,8-DHF is a potential chemical that may alleviate the detrimental effects of the cafeteria diet due to its neuroprotective, antidepressant, and antioxidant characteristics. Its capacity to boost TrkB signaling and safeguard against decline in cognition positions it as a promising subject for further investigation in dietary therapies targeting the enhancement of mental health and cognitive performance in those adhering to unhealthy diets. The neuroprotective properties of 7,8-DHF include its capacity to pass through the blood-brain barrier, enabling it to directly affect the central nervous system positively (13). prolonged treatment of 7,8-DHF is anticipated to enhance synaptic proteins and elevate their expressions.

7,8- DHF may have exhibited its therapeutic properties in two ways:

. as an agonist of the TrkB pathway (15,37,38).
. as anti-inflammatory and antioxidant (39,40).

In our study, an analysis could not be conducted to distinguish these two effects independently. This study revealed the beneficial impacts of 7,8-DHF on behavioral test performance and the reduction of MDA levels in the hippocampus and cortex. Our findings suggest that the cafeteria diet adversely affects brain functions via oxidative stress mechanisms; however, administration of 7,8-DHF may mitigate this damage. The present study has several limitations, such as the absence of molecular validation for BDNF/TrkB signaling, the lack of gender-based analysis, the brief treatment duration, and the restricted behavioral domain. Further studies are required to clarify the impact of the substance on functional decline generated by a cafeteria diet.

This study largely focused on the cortex. Behavioral investigations concerning the cortex were conducted and linked to oxidative stress in the cortex. The degeneration of the hippocampus was already well established. This study demonstrated analogous alterations in oxidative stress inside the hippocampus and the cortex. The hippocampus alterations seen in this study were consistent with findings from earlier research.

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