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ORIGINAL PAPER

Maternal high-fat diet impairs cognitive performance by altering hippocampal GRP78/PERK axis and BDNF expression in adult female rat offspring: the potential protective role of N acetylcysteine

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Abstract

Maternal high fat diet (HFD) affects the neurodevelopment of offspring and has long-term consequences on cognitive behavior. This study investigated changes occurring in GRP78 and PERK, important markers of endoplasmic reticulum stress (ERS) signaling, in the hippocampus of female adult rats exposed to maternal HFD, and in brain-derived neurotrophic factor (BDNF) signaling, with its important role in the regulation of cognitive behavior, and the potential neuroprotective effects of N-acetylcysteine (NAC) against these changes. A maternal obesity model was created with HFD (60% kcal). NAC (150 mg/kg) was administered intragastrically to both the NAC and HFD + NAC groups. The animals were mated at 12 weeks of age. The same diet was maintained throughout pregnancy and lactation. All female rat pups were subjected to the water maze test at eight weeks of age. Hippocampal GRP78 and PERK expressions increased in the HFD rats. However, maternal HFD suppressed hippocampal BDNF levels and reduced hippocampal neuronal volume. NAC supplementation reduced GRP78 and PERK expressions and increased BDNF and hippocampal volume values in the HFD + NAC group. At behavioral assessments, rats in the HFD group exhibited decreased memory and learning ability, but the HFD + NAC group exhibited stronger responses than the HFD group. Our findings suggest that the decrease in BDNF expression, which plays a role in memory and learning, after maternal HFD exposure may be due to ERS associated with increased GRP78 and PERK expressions. Furthermore, NAC supplementation may ameliorate the impairment in memory and spatial learning ability by attenuating hippocampal ERS in HFD rats.

Keywords BDNF · Cognitive performance · GRP78 · PERK · Maternal high fat diet

Introduction

While early neurodevelopmental processes during pregnancy are sensitive to environmental factors, nutritional changes appear to have important effects on the central nervous system (Rafati et al. 2022). An unhealthy maternal diet has been associated with neurodevelopmental disorders in children, including poor cognitive performance in offspring, attention-deficit/hyperactivity disorder, and autism in early and middle childhood (Sanchez et al. 2018). Studies provide evidence that a high maternal body mass index increases the risk of behavioral and neuropsychiatric disorders in children, including autism, anxiety, aggressive behavior, learning disorders, depression and schizophrenia (Mizera et al. 2022). Research has shown that obesity during pregnancy increases oxidative stress in offspring, leading to a chronic inflammatory state in the brain and disruption of the

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prefrontal cortex and hippocampus, impairing learning and memory functions. The heightened risk of obesity due to increased fertility rates and findings concerning the deleterious effects on brain development in offspring of a maternal high-fat diet (mHFD) raises an important question regarding the effects on offspring brain development.

The endoplasmic reticulum (ER) represents the site of folding, post-translational modification, and maturation of secreted and membrane proteins. Studies have shown that obesity or long-term HFD can increase ER load, thus inducing ER stress (Ajoolabady et al. 2022; Soeda et al. 2017). This triggers a signaling pathway known as the unfolded protein response (UPR), causing unfolded or misfolded proteins to accumulate, one of the responses to ER stress (Jangra et al. 2017). UPR activation leads to heightened release of glucose-regulated protein 78 (GRP78), an ER-resident chaperone. Both clinical and animal studies suggest that GRP78 and PERK are essential factor in ER stress for balancing mitochondrial biosynthesis and mitophagy, representing a potential therapeutic target in the context of obesity (Contreras et al. 2018). However, new data on the therapeutic target ERS for obesity and the efficacy thereof remain scarce.

Numerous metabolic stimuli (such as high blood sugar and a high-fat diet (HFD)) can result in the accumulation of unfolded or misfolded proteins in the ER lumen. Experimental studies have shown that ER stress activates the hippocampal region, which plays an important role in the pathogenesis of learning and memory impairment (Zhu 2020). Pinto et al. (2022) showed that early and continuous exposure to a high-sucrose diet induces metabolic syndrome, and that such a diet causes significant hippocampal ER stress characterized by a failure of pro-adaptive signaling. Those authors also showed that this effect subsequently increases the gene expression of Chop and p21, markers of cell death and senescence. This in turn leads to disruption of hippocampal homeostasis and to the early compromise of both motor and cognitive functions in rats. These findings demonstrate the sensitivity of the hippocampus to ER stress. Niu et al. (2022) demonstrated that HFD triggers ER stress activation through increased PERK, eIF2α phosphorylation, and GPR78 expression. They also suggested that ER stress affects the synaptic plasticity of hippocampal neurons and plays an important role in HFD-induced obesity-associated cognitive dysfunction. Obesity-related cognitive impairment is becoming increasingly widely observed and may represent an early symptom of neurodegenerative diseases that requires heightened attention.

ER stress has been implicated in the pathogenesis of various metabolic disorders. However, further research is needed in order to fully explain the pathogenesis of obesity-related cognitive impairment. No relationship between mHFD, ER stress, and the programming of hippocampal development has to date been confirmed. The current study, performed in order to elucidate ERS-induced changes caused by mHFD in the offspring hippocampal region and the associated mechanisms, may shed light on the cross-talk between mHFD, ER stress, and cognitive impairment.

Brain-derived neurotrophic factor (BDNF) is a neurotrophin produced in the ER with important functions in terms of long-term memory, assisting in the survival of various types of neurons, and in the growth and differentiation of new neurons and synapses (Kowiański et al. 2017). Environmental factors such as genetic traits and an unhealthy lifestyle impair BDNF signaling and have been implicated in the pathogenesis of neurodevelopmental processes (Motamedi et al. 2017). Studies show that mHFD leads to serotoninergic, GABAergic, and BDNF alterations in the juvenile hippocampus, resulting in impaired spatial learning and short-term memory in adulthood (Kim and Park 2018). Identifying changes in proteins associated with cognitive activity in the hippocampal region is therefore of considerable importance in terms of elucidating mHFD-induced cognitive impairment.

N-acetylcysteine (NAC) possesses anti-inflammatory, anti-apoptotic, and pro-neurogenic properties (Tardiolo et al. 2018) and has been proposed for neuroprotective use in neurodegenerative disorders and cognitive therapies (Schoeps et al. 2022). The present study investigated whether NAC, a potent antioxidant compound with an important role in mediating the long-term effects of early life stressors, can be used as a preventive strategy by administering it to the mother.

Our review of the current literature showed that this research is the first to address changes in the GRP78/PERK/BDNF axis in adult female rat pups exposed to mHFD stress and to consider the potential therapeutic effect of NAC on spatial learning and memory impaired by these changes. Our objective in clarifying the role of ER stress in the impairment of cognitive activity in rat pups exposed to a high-fat diet during pregnancy and lactation is to serve as a guide to further research into the eradication and treatment of obesity-induced impairments in programmed spatial learning and memory at the cellular level.

Materials and methods

Creating the experimental model

Sixteen female albino Wistar rats (25 days old) were randomly divided into four equal groups. Animals in the standard diet (SD) and NAC groups received a standard diet (10% k/cal), while those from the HFD and HFD+NAC

groups received HFD (60% k/cal) (Kayhan Kustepe et al. 2022). When the animals in all groups reached the age of 12 weeks, they were left to mate with male breeding rats for one day under suitable conditions. Vaginal smear samples were collected the following day, and those animals whose samples contained sperm were considered to be on day 0 of pregnancy. The animals used in the experiment were obtained from and maintained by the Adıyaman University Experimental Animal Research Center, Türkiye, following receipt of approval from the Adıyaman University experimental animal ethics committee (no. 2022/032 dated 26.05.2022). The members of all four groups continued to receive the same diets during pregnancy and lactation. The HFD+NAC and NAC groups were administered NAC (Sigma-Aldrich; Merck) by intragastric gavage at 150 mg/kg between the beginning of pregnancy and postnatal day 25 (Zhang et al. 2017). The dams commenced giving birth approximately 21 days post-fertilization, and were placed in cages together with their pups. The female offspring of dams from each group were assigned into respective groups. At 10 weeks of age, all rats were subjected to the water maze test (WMT) to assess learning and memory. At the end of the experiments, all animals were euthanized by anesthesia using intramuscular ketamine (50 mg/kg) / xylazine (10 mg/kg). The number of animals to be used in the study (eight in each group, 32 pups in total) was determined using the G* power program based on data obtained from previously published studies. Based on findings from our previous study, the effect size was calculated as 0.88 using the G*Power software (Tüfekci et al. 2023a). With an α error probability of 0.05 and a power (1-β error probability) of 0.95, the total sample size was calculated to be 28. Considering a potential dropout rate of 10% during follow-up, the number of subjects was determined to be 32.The right lobes of the brains of all 32 animals were used for stereological analyses, and the left lobes for biochemical analyses. All animals were allowed ad libitum access to water and standard chow from weaning until the end of the experiment.

Morris water maze test

The Morris WMT is used to assess hippocampus-based spatial learning and memory. The test experiments commenced 24 h after receipt of the final drug doses. The WMT apparatus consisted of a circular pool (26±2 °C), 150 cm in diameter and 60 cm deep. A hidden platform with a diameter of 10 cm was placed 1.0–2.0 cm below the surface of the water and maintained at this level, which the rats were able to locate using environmental cues. Colorful geometric shapes or pictures were hung on the walls of the room where the test was conducted in such a way that the animals could see them through the water. Each rat was allowed to establish the relationship between the environment and the platform and to locate the platform using environmental cues. None of the objects in the room were moved during the course of the experiment. All experiments were performed by the same researcher, in accordance with the study protocol, with no changes of clothing. The rats were released into the pool from a different location every day, after which they were expected to find the platform within 60 s. If a rat was unable to find the platform, it was placed on it manually, left there for 10 s to recognize its environment, and then returned to its cage. The rats were subjected to five consecutive experiments per day, totaling 20 experiments in four days. On the fifth day, 24 h after the end of the learning experiments, each animal underwent a probe trial. This involved the platform being removed from the pool and the rat being permitted to swim freely for one minute. The amount of time spent in the quadrant where the platform had previously been located was recorded. A camera was installed directly over the pool in order to monitor the animals during the trials. Behavioral data were evaluated using the Ugo Basil water maze tracking system. The time taken to find the platform, swimming speed, and the length of time spent in the target quadrant were determined.

Tissue preparation

At the conclusion of the experiment, the rat brain tissues were fixed with 10% formaldehyde solution and subjected to routine histological procedures for light microscopic analysis. The tissues were then embedded in paraffin blocks. Next, 7 µm-thick sections were taken for histopathological examinations and 5 µm-thick sections for immunohistochemical analyses (Thermo Fisher Scientific, Cheshire, UK). Brain sections were stained with cresyl violet for histopathological analysis and examined under a light microscope. All images were captured by projection onto a computer screen using a light microscope with a digital color camera attachment (Carl Zeiss Microscopy GmbH 07745 Jena, Germany).

Immunohistochemical staining and scoring

Briefly, 5 µm thick brain tissue sections were mounted on polylysine slides. After deparaffinization, the sections were kept in sodium citrate for antigen retrieval. To block endogenous peroxidase activity, the slides were incubated in 3% hydrogen peroxide solution for 20 min. Then, they were washed three times with phosphate buffer solution (PBS) for 15 min. Ultra V Block solution was applied to prevent nonspecific protein binding. Tissues were then exposed to Grp78 (Proteintech, catalog number 1587–1-AP) (1:200) and PERK (Proteintech, catalog number 24390–1-AP)

(1:200) antibodies overnight at 4 °C. Following incubation, biotinylated secondary antibody was dropped onto sections washed with PBS and incubated in streptavidin-HRP complex for 30 min after the washing step. Finally, DAB chromogen was used to visualize the antigen–antibody complex. Slides were counterstained with Gill's hematoxylin and coverslipped with Entellan using a coverslip.

The prepared slides were examined under a light microscope using X5, X10, X20 and X40 lenses and the presence of red color was considered as a positive reaction. Staining intensities in all sections were scored based on a semi-quantitative method. The intensity of immunopositive cells in the CA1, CA3 and dentate gyrus (DG) regions of the hippocampus was evaluated as (-), no staining, (+), weak, (++), moderate, and (++ ++), strong staining. The range of possible scores was from 0 to 3. The expression level of each component was categorized as low or high according to the H-score median value. All parameters were independently evaluated by a specialist histologist blinded to the study groups. Histo-scoring (H-score), representing a semi-quantitative analysis of immunohistochemical scoring, staining intensity, and percentages, was also performed (Tüfekci et al., 2023a).

Stereological analysis

Estimation of hippocampal CA1, CA3 and DG volume

The volumes of the CA1, CA2, CA3 and DG regions of the hippocampus were calculated from the brain tissues using the Cavalieri method. Briefly, 5 µm-thick sections were taken from each brain tissue at a sampling rate of 1/50 in line with the systematic random sampling rule and stained with cresyl violet. These were then photographed under a light microscope for volumetric analysis (Carl Zeiss Microscopy GmbH 07745 Jena, Germany). The Cavalieri method is based on multiplying the surface area of the object under examination by the average section thickness. A dot-counting ruler was used to calculate the surface areas. These were calculated on Image J (Image Processing and Analysis in JAVA, NIH, USA) software using the stereological point counting method by randomly placing regular grid test points (corresponding to the ARC core) over cross-sectional tissue images. Once the surface areas had been calculated, volumetric values were estimated using the following formula;

$$Vref = \sum Pi \times t$$

$$Pi = P(a)$$

$$\sum V = V1 + V2 + V3 + \cdots$$

where "Vref" is the total or reference volume of the structure of interest, '∑Pi' is the total number of points in each cross-section, 'P(a)' is the area represented by a single point on the point counting ruler, 't' is the average cross-section thickness, and 'V' is the volume of a tissue cross-section. After applying the same formula for all sections, the volumes were summed to yield the total volume (Kocaman et al. 2017).

Biochemical analysis

Brain tissue specimens from all four groups were stored at -80° C. All brain tissue samples were homogenized in phosphate buffer (pH 7.2–7.4). The homogenates were then centrifuged at 5000xg for 5 min at 4° C to obtain the supernatant. BDNF levels were measured by means of the enzyme-linked immunosorbent assay (ELISA), using the supernatant obtained from brain homogenates after centrifugation with a BDNF ELISA kit (rat BDNF ELISA kit, ab213899) according to the manufacturer's instructions. BDNF levels were expressed as pg/ml.

Statistical analysis

Numerical data were analyzed using SPSS software (SPSS version 21.0; SPSS Inc., Chicago, IL, USA) and expressed as mean±standard deviation. Normality (Shapiro–Wilk) and homogeneity tests confirmed that all four groups followed a normal distribution. Differences between groups were compared using one-way ANOVA. Tukey's post hoc test was applied for multiple comparisons. The results were evaluated within a 95% confidence interval, and a p-value of <0.05 was considered statistically significant.

Results

Stereological results

Hippocampal volume values

The volumes of the hippocampal subregions (CA1, CA3 and DG) were analyzed using the Cavalieri method. Analysis of the CA1 region revealed that the volumetric values in the HFD group were significantly lower than those in the SD and HFD+NAC groups ($p=0.007$, $p=0.023$, respectively). No significant difference was detected between the HFD group and the NAC group in terms of CA1 region volumes ($p=0.18$) (Fig. 1b). However, a statistically significant decrease in CA3 volume values was observed in the HFD

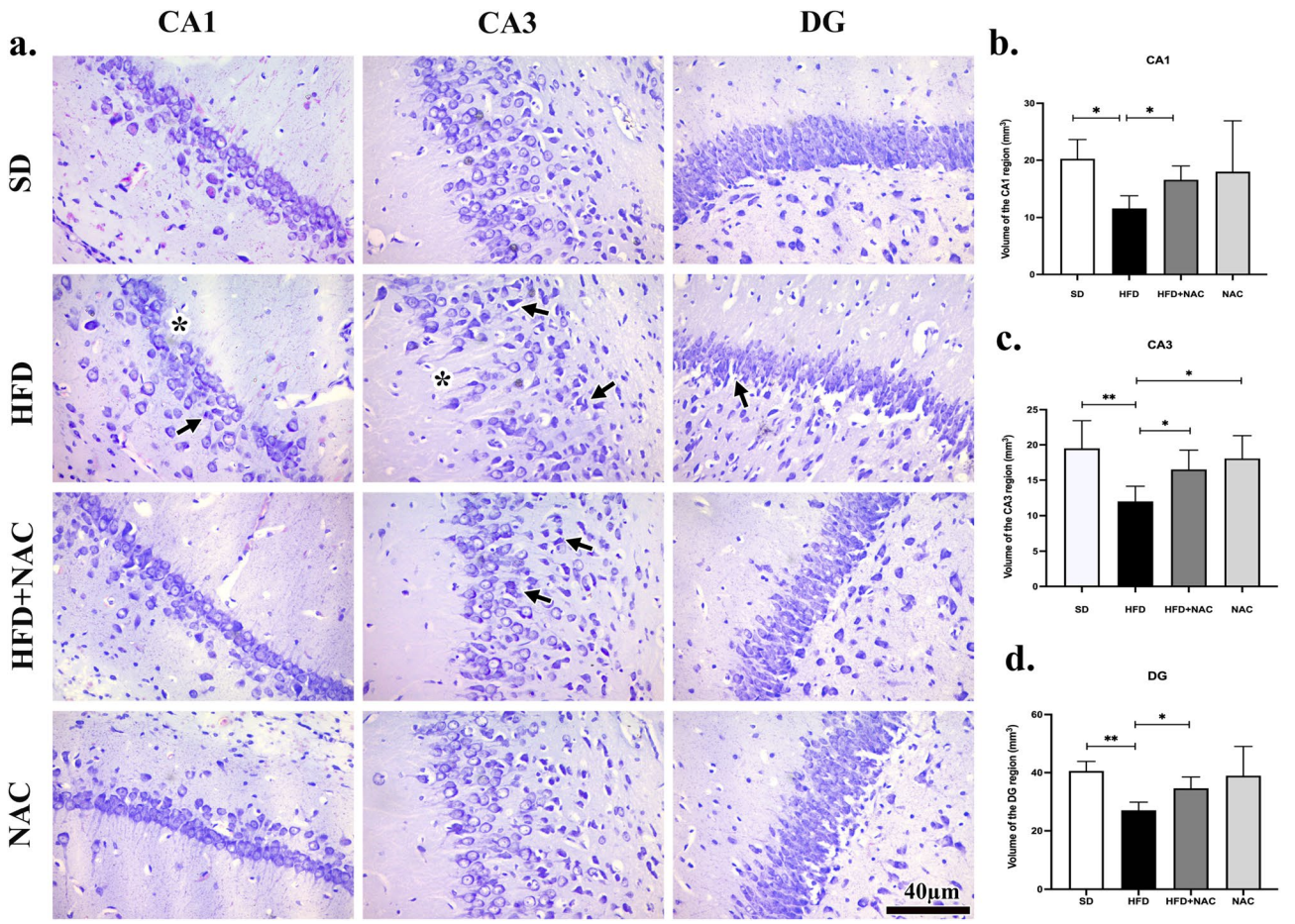

Fig. 1 (**a**), Images of cresyl violet staining in the cornu ammonis (CA) and DG regions of the hippocampus. SD, NAC, and HFD+NAC groups: a normal histological structure can be seen in pyramidal and granular formations. HFD group: degenerated neurons (black arrows), intercellular spaces (*). **b-d**, Graph showing stereological volumetric analyses in the CA1, CA3 and DG regions of the hippocampus. Differences that are statistically significant at the $p<0.05$ level are indicated by "*", and those significant at the $p<0.01$ level by "**" (mean±SD)

group compared to the SD, HFD+NAC and NAC groups ($p=0.040$, $p=0.023$, and $p=0.003$, respectively) (Fig. 1c). The volume of the DG region in the HFD group was significantly lower than those in the SD and HFD+NAC groups ($p\leq0.001$ and $p=0.021$, respectively). Similarly to the CA3 region, NAC supplementation reversed the mHFD-induced decrease in the DG region (Fig. 1d). Our results suggest that mHFD reduces CA1, CA3 and DG region volumes, while NAC supplementation reverses the adverse effect of mHFD.

Histopathological results

Histopathological analysis of the CA1 and CA3 regions of the hippocampus showed that the nuclei and cell boundaries of the neurons in the SD and NAC groups were distinct, with a healthy appearance (Fig. 1a). In contrast, the HFD group exhibited numerous pyramidal neurons with darkly stained, indistinguishable nuclei and unclear cell boundaries. These were interpreted as apoptotic neurons that had lost their functions. Irregular neuron arrangement and intercellular spaces were especially pronounced in the CA1 region. In addition, the arrangement of pyramidal cells was irregular in the HFD group, with numerous intercellular spaces with fewer layers in this region compared to the other groups (Fig. 1a). Light microscopic images of the CA1 and CA3 regions of the groups exposed to NAC treatment after mHFD exposure revealed that, despite the presence of a few darkly stained neurons with indistinct nuclei, the primal neurons largely preserved their healthy appearance (Fig. 1a). The cell layer numbers in the pyramidal neurons in these treatment groups were similar to those in the SD group. Examinations of the DG region of the hippocampus revealed tightly packed granular cells with distinct nuclei in the SD, NAC, and HFD+NAC groups. In contrast, the granular neurons in the HFD group were degenerated, the cells were darkly stained, and the cell borders could not be distinguished. In addition, the number of cell layers in this layer was lower than in the SD, HFD+NAC, and NAC groups (Fig. 1a).

Immunohistochemical results

GRP78 immunohistochemical staining

Cells exhibiting red or dark staining were regarded as positive at immunohistochemical examinations using GRP78 antibodies in the CA1, CA3 and DG regions of the hippocampus. While weak GRP78 immunoreactivity was observed in the pyramidal cell layer in the CA1 and CA3 regions from the SD, NAC, and HFD+NAC groups, pyramidal neurons from the HFD group exhibited strong GRP78 positive staining. A moderate level of GRP78 immunoreactivity was determined in the DG regions from the SD, HFD+NAC, and NAC groups, especially in the polymorphic cell layer. Granular cells in the DG regions from the HFD group were widely stained and exhibited strong immunoreactivity (Fig. 2a). Semi-quantitative scoring revealed significantly more anti-GRP78 (+) cells in the CA1 region of the hippocampus in the HFD group compared to the SD, HFD+NAC, and NAC groups ($p \leq 0.001$, $p = 0.025$, and $p = 0.003$, respectively) (Fig. 2b). Anti-GRP78 (+) cell scores in the CA3 region were significantly lower in the SD group compared to the HFD group, while no significant difference was observed between the HFD+NAC and NAC groups and the HFD group ($p = 0.008$, $p = 0.016$, and $p = 0.093$, respectively) (Fig. 2c). Anti-GRP78 (+) cell scores in the DG region were significantly higher in the HFD group than in the SD, HFD+NAC and NAC groups ($p = 0.002$, $p = 0.017$, and $p = 0.004$, respectively) (Fig. 2d). To summarize, NAC treatment in the CA1 and DG regions preserved GRP78 expression levels in the HFD+NAC group.

PERK immunohistochemical staining

Cells exhibiting red or dark staining were regarded as positive at immunohistochemical examinations using PERK antibodies in the CA1, CA3 and DG regions of the hippocampus. While weak PERK immunoreactivity was observed in the pyramidal cell layer in the CA1 and CA3 regions from the SD, NAC, and HFD+NAC groups, pyramidal neurons from the HFD group exhibited strong

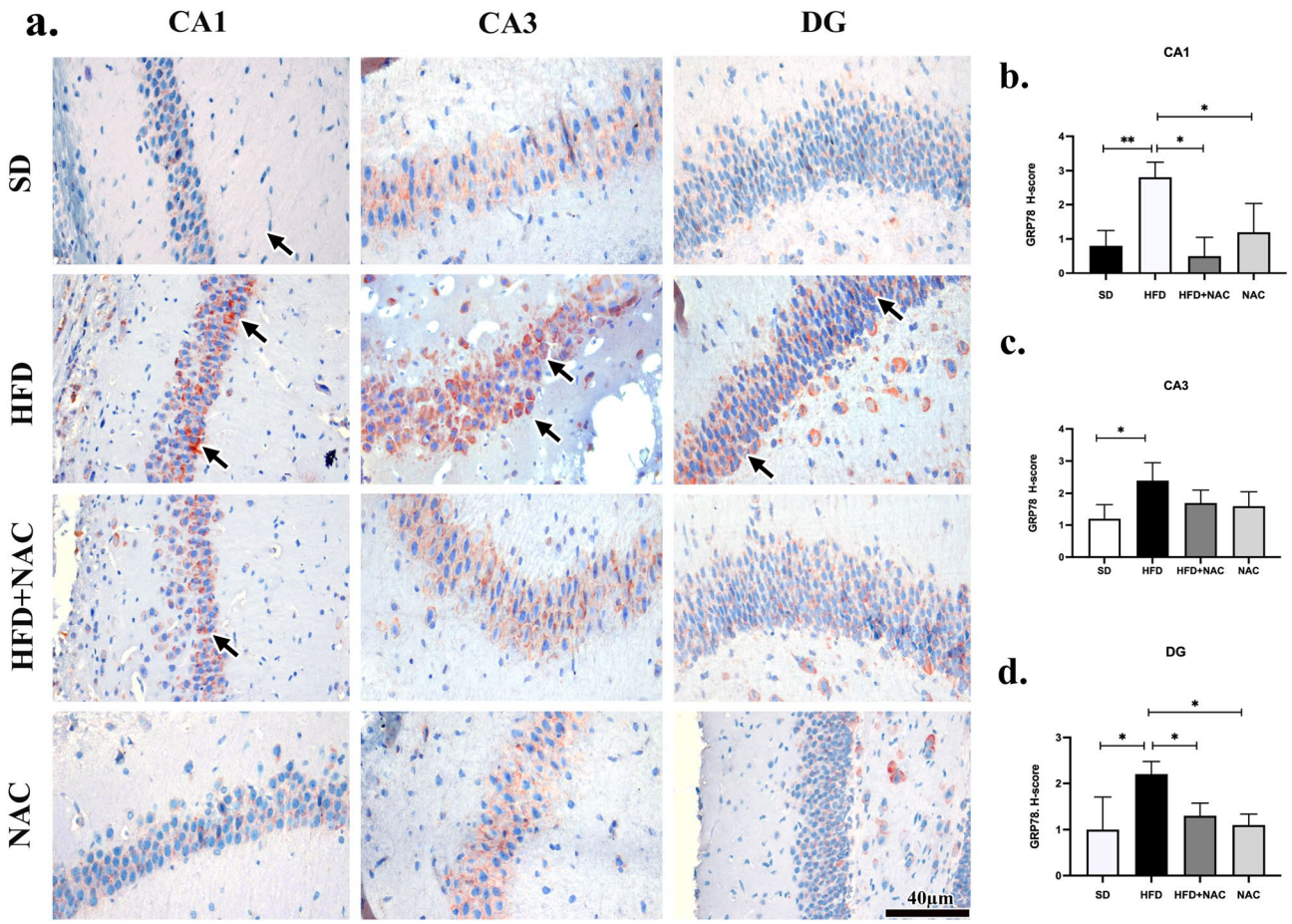

Fig. 2 (**a**), Immunohistochemical staining of the cornu ammonis (CA) and DG regions of the hippocampus. Black arrows indicate cells with strong anti-GRP78 (+) staining. **(b-d)**, IHC scores of anti-GRP78 (+) cells of the CA and DG regions in all groups. Differences significant at $p < 0.05$ are indicated by "*" and differences significant at $p < 0.01$ by "**" (mean ± SD)

PERK positive staining. A weak level of PERK immunoreactivity was determined in the DG regions from the SD, HFD+NAC, and NAC groups, especially in the polymorphic cell layer. Granular cells in the DG regions from the HFD group were widely stained and exhibited strong immunoreactivity (Fig. 3a). Semi-quantitative scoring revealed significantly more anti-PERK (+) cells in the CA1 region of the hippocampus in the HFD group compared to the SD, HFD+NAC, and NAC groups ($p \leq 0.001$) (Fig. 3b). Anti-PERK (+) cell scores in the CA3 region were significantly lower in the SD and NAC groups compared to the HFD group, while no significant difference was observed between the HFD+NAC group ($p \leq 0.001$, $p = 0.089$, and $p = 0.002$, respectively) (Fig. 3c). Anti-PERK (+) cell scores in the DG region were significantly higher in the HFD group than in the SD, HFD+NAC and NAC groups ($p \leq 0.001$, $p = 0.007$, and $p \leq 0.001$, respectively) (Fig. 3d). To summarize, NAC treatment in the CA1 and DG regions preserved PERK expression levels in the HFD+NAC group.

Biochemical results

Biochemical analysis revealed significantly higher BDNF values in the SD group compared to the HFD group ($p \leq 0.001$) BDNF values were also significantly higher in the HFD+NAC and NAC groups compared to the HFD group ($p = 0.005$). However, no significant differences were observed between the SD, NAC, and HFD groups ($p \leq 0.001$) (Fig. 4a).

Water maze test

All animals from all groups completed the test procedure. Analysis of the WMT results revealed a significant decrease in learning and memory performances in the HFD pups compared to the SD pups. No significant differences were determined between the groups in terms of swimming speed (Fig. 4c). The HFD adult pups took longer to locate the platform than those from the SD and NAC pups. These results show that learning functions were adversely affected. However, it took the HFD+NAC group significantly less time

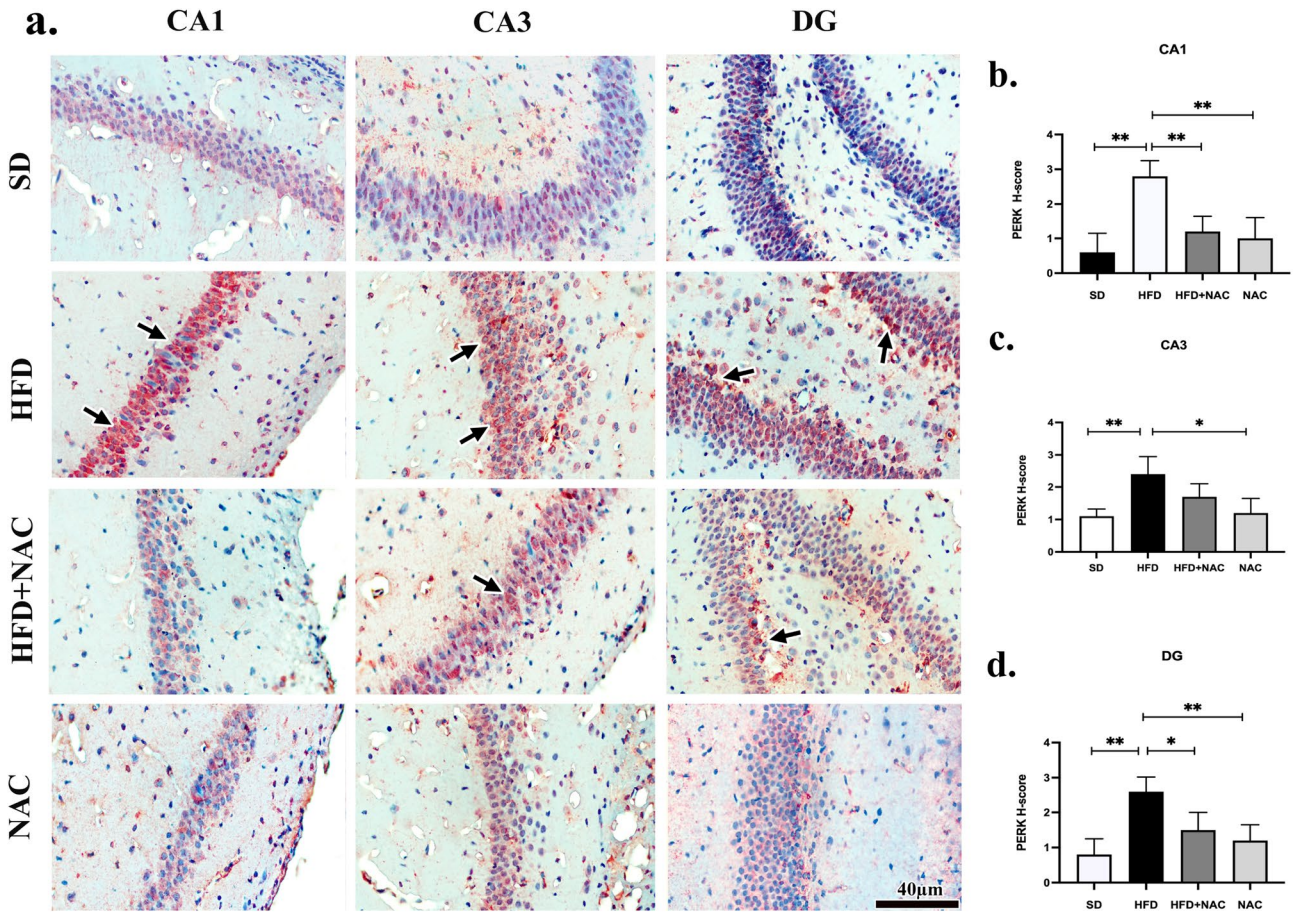

Fig. 3 **(a)**, Immunohistochemical staining of the cornu ammonis (CA) and DG regions of the hippocampus. Black arrows indicate cells with strong anti-PERK (+) staining. **(b-d)**, IHC scores of anti-PERK (+) cells of the CA and DG regions in all groups. Differences significant at $p < 0.05$ are indicated by "*" and differences significant at $p < 0.01$ by "**" (mean ± SD)

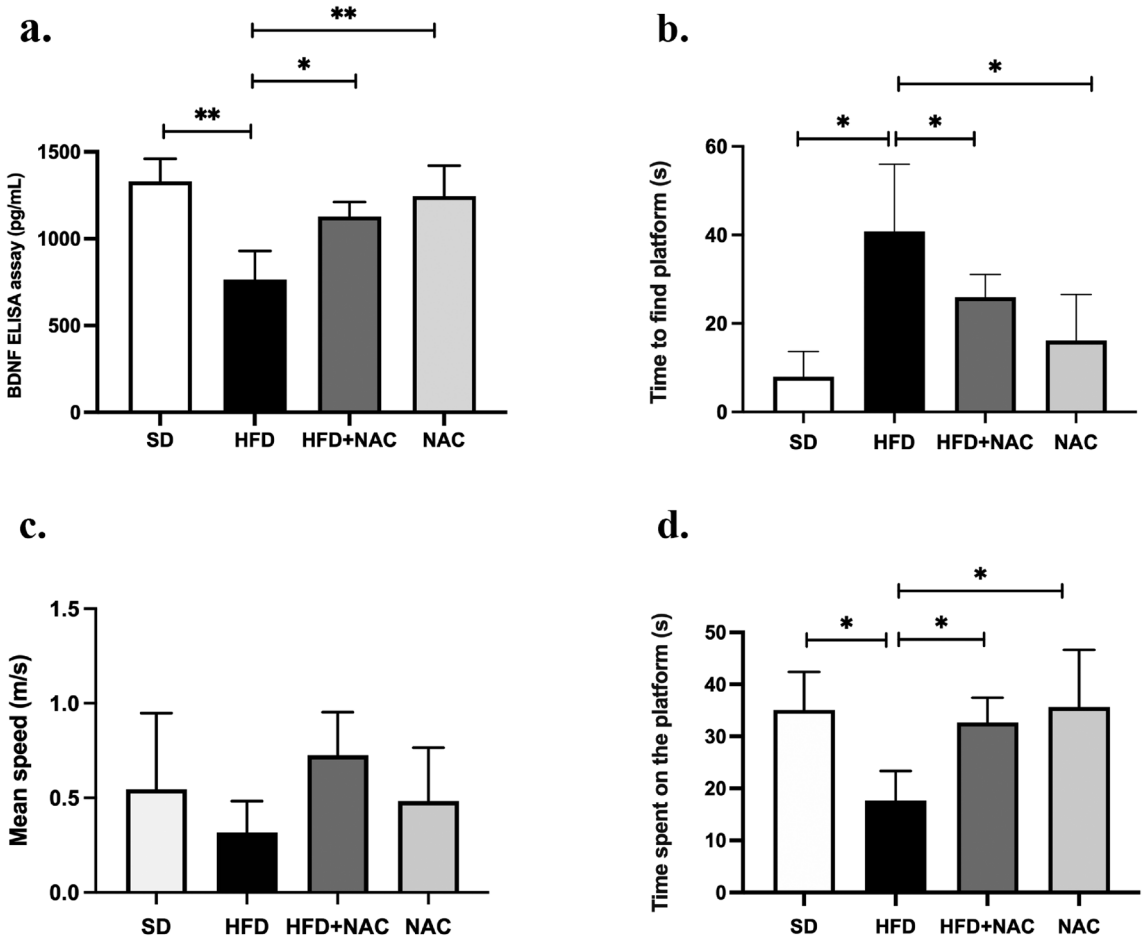

Fig. 4 (**a**), graph showing the hippocampal BDNF levels in all four groups. **(b-d)**, graphs showing the WMT learning and memory performances at the end of the experiment. Differences significant at $p<0.05$ are indicated by "*," and those significant at $p<0.01$ by "**" (mean ± SD)

to reach the platform than the HFD group. This shows that NAC can reverse adverse effects on mHFD learning performance (Fig. 4b).

Similarly, in the recall (probe trial) experiment conducted on the fifth day when memory performance was evaluated, the time spent in the target quadrant (learning the location of the platform) was shorter in the HFD adult pups compared to the SD, NAC and HFD + NAC groups, indicating that HFD exposure may cause memory problems in adult pups. The greater time elapsing in the target quadrant among the HFD adult offspring receiving NAC supplementation suggests that this may prevent mHFD-derived memory problems (Fig. 4d).

Discussion

The evidence yielded by this study supports the hypothesis that maternal obesity impairs cognitive function. The research focused on the impacts of maternal obesity on hippocampal ER stress and BDNF levels in adult female rat offspring. The study hypothesis was confirmed by water maze analysis demonstrating the deleterious consequences of mHFD on learning and memory. The findings indicated that mHFD promotes an environment that associates ER stress with increased GRP78 and PERK accompanied by decreased BDNF expression in adult offspring. The results also confirm the idea that NAC supplementation can largely mask the adverse impacts on learning and memory by effectively targeting a mechanism associated with ER stress.

There are several hypotheses that the hippocampus, a critical organ in the context of learning and memory, is vulnerable to nutritional deficiencies in early life. However, little is known about the mechanisms linking maternal obesity to neurochemical changes and cognitive impairment in offspring. Current research focuses on changes in BDNF levels as a first step in explaining this phenomenon (Bae-Gartz et al. 2019; Hsu et al. 2020).

Studies have shown that BDNF, which is important for hippocampal neurogenesis, is particularly sensitive to early life disorders. Current data suggest that prenatal exposure to maternal obesity is associated with decreased levels of

BDNF, which is important for hippocampal neurogenesis, abnormal dendritic differentiation, and abnormal hippocampal development of newly formed neurons during early postnatal development (von Bohlen und Halbach, 2018; Basalai ve ark., 2020; Hsu ve ark., 2020).

A previous study showed that hippocampal granule cells exhibit abnormal morphological development with fewer and shorter dendritic branches in case of BDNF deficiency (von Bohlen und Halbach, 2018). In the present study, the presence of hippocampal neurons exhibiting loss of function and a non-normal morphology in the offspring exposed to mHFD suggests that downregulation of BDNF induces morphological changes at the cellular level. BDNF may therefore perform an important function in protecting the postnatal brain, and BDNF signaling irregularities may be associated with morphological changes potentially linked to pathophysiological states.

The present study revealed a decrease in the volumes of the hippocampal CA1, CA3 and dentate gyrus regions in HFD adult female offspring. Shiadeh et al. (2024) in their stereological study examining the long-term effects of maternal obesity on the hippocampus of their offspring, Shiadeh et al. (2024) reported that offspring of obese mothers exhibited significantly reduced hippocampal volume and cortical thickness compared to offspring of lean mothers. Similarly, our previous study involving male offspring of rats exposed to mHFD during pregnancy showed that maternal obesity can affect a number of behavioral patterns by causing a volumetric reduction in hippocampal neurons (Tüfekci et al., 2023a). Thus, early adversities may affect neurogenesis in the hippocampus, leading to long-term volumetric neuronal reduction (Page et al. 2018; Na et al. 2021).

Fusco et al. (2019) showed that mHFD-induced insulin resistance downregulates BDNF and insulin signaling in maternal tissues across generations and epigenetically suppresses BDNF expression in both the germline and offspring hippocampus. Our results confirm those reported by Fusco et al. (2019), who examined the long-term effects of maternal obesity on the hippocampus. All these results suggest that mHFD exposure has a transgenerational effect and that downregulation of BDNF results in reduced neurogenesis, which may have negative consequences on long-term cognitive behavior and spatial learning.

In contrast to our findings, Dias et al. (2020) suggested that mHFD stimulated the proinflammatory pathway and increased the expression of tryptophan hydroxylase 2 (TPH2) and BNDF in the adolescent mouse hippocampus (Dias et al. 2020). The main reason why changes in BDNF levels under the effect of mHFD are unclear may derive from differences in the composition of the diet applied in the studies, the period of exposure, and the duration of the diet, which represents an important factor limiting the generalizability of the results (Dias et al. 2020).

Analysis of the WMT results in the present study revealed significant impairments in learning and memory performance, i.e. neurocognitive functions, of HFD adult female offspring. Since spatial learning and memory depend on changes in the hippocampal region, dietary manipulations during development are likely to affect key neurotrophins that mediate cognitive performance (Page et. al, 2014). The study data are consistent with this hypothesis since the compromises observed in spatial learning and memory in HFD adult offspring were accompanied by decreased BDNF levels in the hippocampal regions. Similarly, mHFD/obesity has been shown to suppress adiponectin, phosphorylated alpha serine/threonine protein kinase (pAKT), sirtuin 1 (SIRT1), and BDNF in the rat placenta, male fetal brain, and dorsal hippocampus of adult male offspring, and resulted in significant impairments in acquisition and retention in the Morris WMT (Hsu et al. 2020). Although the direct relationship between these findings needs to be further examined, BDNF mediates the structural and/or functional plasticity of the hippocampus in adult HFD offspring.

A recent meta-analysis examining results from animal models suggested that maternal obesity has significant effects on locomotor activity and anxiety, but no significant impacts on learning or memory performance (Menting et al. 2019). The differences between the study results may be attributable to the period when the tests were applied (breastfeeding, adolescent, or adult) or to changes in the MWM protocols (in the number of test trials). Changes in the environment or the animal feeling uncomfortable or afraid of its environment may affect its learning performance. Care was therefore taken in the present study to avoid changes in the environment that might lead to deterioration in learning performance.

The majority of studies evaluating the effects of maternal obesity on the brain are limited to male rodents in order to avoid changes affected by gonadal hormones and in sexual receptivity. In order to address this knowledge gap, the present study set out to examine the impact of ER stress on cognitive and emotional functions and the involvement of BDNF in adult offspring female rats exposed to mHFD. In their study investigating the gender-specific effects of exposure to in utero obesity on hippocampal volume in children aged 7–11 years, Alves et al. (2020) observed a decrease in hippocampal volume in boys, but no comparable effect in girls. The growth trajectories for hippocampal volume differ between the sexes. Due to the cross-sectional design of this research, whether or not the association observed predominantly in boys will persist throughout life is unclear. Gender differences should therefore be considered when evaluating the effects on cognitive development of maternal obesity

exposure during early developmental periods. Also, the results of studies examining the effects of maternal obesity on cognitive behaviors in female rats are contradictory in the literature. Graf et al. demonstrated sex-dependent effects of maternal HFD and observed that HFD exposure impaired novel object recognition in male offspring but not in female offspring (Graf et al., 2016). Underwood and Thompson in their study observed deficits in spatial object recognition memory associated with impaired hippocampal function in female young adult rats subjected to a high-fat diet (Underwood and Thompson, 2016). However, the insufficient number of studies conducted on female subjects in the existing literature limits the comparability of our results. Therefore, considering the studies in the literature, we believe that more studies involving male and female subjects are needed to explain the ambiguity of gender-based differences.

A growing body of evidence suggests that metabolic disturbances cause ER stress, thereby leading to synapse dysfunction and neurodegeneration (Nakagawa et al. 2022). In our study, we identified the contribution of the GRP78/PERK axis, an important marker of ERS signaling, to hippocampal spatial learning and memory impairment in mHFD. In particular, GRP78, known as a master regulatory protein of the UPR, can induce apoptosis through the expression of C/EBP homologous protein (CHOP) in long-term unresolved ER stress. Notably, recent evidence has reported that chronic and excessive hippocampal ER stress and upregulation of GRP78 expression also play an important role in memory impairment and hippocampal damage (Cai et al., 2016; Gupta et al. 2021). However, several lines of evidence have suggested that sustained activation of PERK impairs cognitive function by suppressing the expression of key proteins involved in neuronal plasticity and memory formation (Ohno 2018; Taalab et al. 2018). Similarly, our previous study demonstrated increased expression of Grp78, PERK and eIF2α, important markers of ERS, in hippocampal CA1 and DG regions in male offspring exposed to mHFD (Tüfekci et al., 2023b). The data of the present study showed that GRP78 and PERK expressions increased in hippocampal cells of HFD adult female offspring after mHFD exposure, indicating that mHFD activates the ERS, which compromises cognitive performance.

Studies suggest that obesity may aggravate oxidative stress and ER stress in cells by increasing the expression of inflammatory response proteins. This may in turn inhibit neuronal stem cell proliferation, reduce the neurogenesis and survival of newly developing neurons, and exacerbate apoptosis in existing neurons (Liu et al. 2019). Kong et al. (2018) showed that neuronal damage occurred mostly in the hippocampus of mice with streptozotocin-induced diabetes. Pathological changes such as a reduced neuronal density, dysfunctional synaptic plasticity, damaged mitochondria, and increased apoptosis were also observed. Simultaneously, those authors observed high IPERK and JNK phosphorylation levels, and high GRP78 and CHOP levels in the diabetic hippocampus. They also observed that the pharmacological inhibition of ER stress reduced high glucose-induced autophagy and apoptosis in primary hippocampal neurons. The results of the present study, consistent with the significant volume loss in the hippocampal region where GRP78 and PERK expressions increased in mHFD rats, suggest that ER stress induced by mHFD may alter the balance of metabolic processes that program neuron formation and development.

This study yielded data consistent with our hypothesis that hippocampal ER stress reduces the production of BDNF, which plays an important role in neuronal development. Hippocampal BDNF levels were significantly lower in the mHFD-exposed rats compared to the SD rats.

There is evidence to show that HFD-induced obesity reduces hippocampal cyclic AMP-response element binding protein (CREB) phosphorylation, as well as BDNF expression, an important step in protein synthesis (Zhong et al. 2016). CREB activation depends on p38 MAPK and ERK activation, and phosphorylation of p38/ERK-CREB plays a role in various physiological processes in neurons, learning, and memory formation (Moosavi et al. 2015). Cai et al. (2016) suggested that hippocampal ER stress, which they demonstrated with increased GRP78, PERK, IRE1α, and eIF2α expressions in the hippocampus due to excess glucose and lipid intake, may reduce BDNF expression by negatively regulating the p38/ERK-CREB pathways. In support of that study, our own results suggest that mHFD induces ER stress in offspring with increased GRP78 and PERK expressions in the hippocampal region, and that such stress may play a role in cognitive and memory impairments associated with maternal obesity by reducing BDNF expression in hippocampal neurons.

Despite the growing body of evidence verifying the role of ER stress in regulating hippocampal neurotrophins, to date no direct link has been established between ER stress and hippocampal BNDF programming under maternal obesity pressure. This study is original from that perspective. However, a number of limitations also need to be considered when interpreting our findings. In particular, we were unable to examine in detail the direct regulatory mechanisms between ER stress and hippocampal BNDF programming under maternal obesity exposure in terms of genes and proteins. More detailed research involving different techniques is now needed to shed light on these molecular pathways. We intend to design further studies to address these limitations.

High-calorie diets trigger ER stress responses in nerve cells by inducing protein misfolding and inflammatory

factors, leading to oxidative stress and neuronal apoptosis. Park et al. showed that monosodium glutamate decreased the increased levels of XBP1, CHOP, PERK and GRP78 in neuroglia cells, indicating a protective role of NAC in cells (Park et al. 2014). Similarly, in our study, decreased GRP78 and PERK levels in the hippocampus of Nac-supplemented HFD adult females support the idea that Nac protects against mHFD-induced hippocampal ER stress. Although experimental studies have shown that NAC supplementation ameliorates cellular changes by lowering oxidative stress levels in the hippocampus, studies investigating the potential effects of NAC on hippocampal ER stress are scarce. Saha et al. (2023) showed that hyperactivation of cyclin-dependent kinase 5 (Cdk5) associated with diabetes may contribute to cognitive disorders by leading to ER stress and activation of the UPR pathway. However, they observed that NAC and GSH were capable of reducing dysregulated Cdk5 kinase activity and protecting cells from UPR-mediated ER stress, thus improving memory and learning disorders. A previous study reported that NAC significantly reduced GRP78 and CHOP expression by inhibiting ROS generation in H9c2 cells and ameliorated oxidative stress-induced ER stress (Yang et al. 2019).

This study tested the effect of maternal NAC supplementation in mHFD on spatial learning and memory. The effects of NAC treatment on learning and memory have also been described in previous studies (Costa et al. 2016). One piece of research showed that NAC administration for eight days following the induction of temporal lobe epilepsy modulated the levels of the protein mammalian target of rapamycin (mTOR), which controls cell growth and proliferation, significantly increased the number of CA3 neurons in the hippocampus, and demonstrated a potential effect on improving memory loss in rats (Mohammadi et al. 2023). Similarly in the present study, the neuronal volume loss in the hippocampal CA1, CA3, and DG regions of mHFD rats improved after NAC supplementation. Our stereologic results also supported the idea that NAC treatment exhibited a protective role in terms of hippocampus volume in the HFD+NAC group. In our study, NAC may have had a decreasing effect on the activation of ER stress markers by reducing the formation of reactive oxygen species, but the fact that we did not use oxidative stress and apoptosis markers in our study can be considered as a limitation of our study.

A considerable body of evidence shows that NAC exerts its neuroprotective effect through various different mechanisms. Musillo et al. (2021) observed that NAC supplementation improved social behavior and restored decreased hippocampal BDNF levels in adolescent mice exposed to HFD. Similarly in the present study, NAC supplementation preserved hippocampal BDNF levels in HFD adult female rats. This effect of NAC on BDNF levels may have reversed the effect of HFD-related volumetric reduction in the hippocampal region.

In addition, in the water maze analyses, the shorter time taken for HFD adult female rats to reach the platform and the longer time spent on that platform after receipt of NAC supplementation suggest that NAC may compensate for the negative effects of mHFD on learning and memory performance.

We attribute the neuroprotective effect of NAC to the ability of obese mothers to prevent the increase in hippocampal ER stress markers observed during lactation. Although there are studies demonstrating the positive aspects of NAC use in both prenatal and postnatal periods through different exposures (Bernhardt et al. 2018; Jenkins et al. 2015), the timing and duration of NAC supplementation is particularly important for clinical applications. Especially in prenatal use, placental metabolism and transfer, as well as pharmacokinetics in the fetus and mother should be taken into account.

Conclusion

In conclusion, the exact mechanisms underlying ER stress in the hippocampus of HFD adult female offspring are still unclear. However, we identified the involvement of GRP78 and PERK activation in neuronal dysfunction and neurodegeneration by also reducing BDNF production under certain pathogenic conditions. Considering these effects of mHFD-induced ER stress on the hippocampus, we believe that these findings are of great importance. New treatments targeting hippocampal ER stress therefore need to be developed. Considered together, our findings suggest that NAC reduces ER stress in adult offspring rats exposed to mHFD stress, preserving BDNF levels and cell survival. They also indicate that NAC may represent a promising therapeutic strategy for treating maternal obesity-associated cognitive disorders. However, the way in which NAC reduces ER stress remains unclear, and further research is needed to clarify exactly which mechanisms are involved.

Author contributions EGB; Creating the experimental model, obtaining data, data collection, formal analysis, article writing. KKT: Fund acquisition, project management, data collection EMBY: Creating the experimental model, performing the WMT. FB: obtaining data, statistical analysis SS: Biochemical analysis.

Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

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