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Original Research

Effect of Hyperbaric Oxygen Treatment on Lipid Metabolism and Neurovascular Microenvironment in an Apolipoprotein E Knockout Mouse Model

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Abstract

Background: Dyslipidemia during midlife represents a significant risk factor for neuropathological alterations associated with cognitive decline. Given the currently incurable nature of dementia, implementation of preventive strategies and early therapeutic interventions prior to disease progression are paramount. Emerging evidence suggests that hyperbaric oxygen (HBO) therapy exhibits neuroprotective properties in various neurological conditions. However, whether HBO treatment modulates lipid metabolism dysregulation and subsequent neurodegeneration remains unanswered. This investigation aimed to elucidate the therapeutic potential of HBO treatment in ameliorating cerebral dysfunction and metabolic perturbations using apolipoprotein E (ApoE)-deficient ($ApoE^{-/-}$) mice. **Methods**: $ApoE^{-/-}$ mice received HBO treatment for 10 consecutive days, and then behavioral assessment tests were performed. Serum and brain tissue were collected to measure oxidative stress levels and inflammatory factors. **Results**: Compared with $ApoE^{-/-}$ group, cognitive declines was significantly reversed in mice of the $ApoE^{-/-}$+HBO mice. The blood lipid profiles of $ApoE^{-/-}$ mice were also improved after HBO treatment, accompanied by a reduction in body weight. Moreover, HBO treatment was found to ameliorates neuronal injury and amyloid-β deposition in the hippocampus of $ApoE^{-/-}$ mice. Further studies have revealed that the benefits of HBO treatment occurred through the reduction of inflammatory factors and attenuation of oxidative stress. **Conclusions**: These findings indicate that HBO treatment effectively improves the intracerebral microenvironment of $ApoE^{-/-}$ mice, providing a novel regulatory mechanism of protection against dyslipidemia-associated brain deficits by HBO treatment.

Keywords: hyperbaric oxygenation; apolipoprotein E; dyslipidemias; cognitive dysfunction; inflammation

1. Introduction

Alterations to the plasma lipid profile characterize dyslipidemia, defined as an elevation of serum total cholesterol (TC), triglycerides (TG), low-density lipoprotein-cholesterol (LDL-C) or reduced high-density lipoprotein cholesterol (HDL-C). The prevalence of dyslipidemia is rising among young people as living standards rise. Dyslipidemia is a chronic systemic condition that has the capacity to significantly contribute to various serious health complications, including obesity, atherosclerosis, and stroke [1,2]. Existing evidence indicates comorbidity or some form of connection between dyslipidemia and central nervous system disorders, such as dementia and Parkinson's diseases [3–5]. A comprehensive assessment of this relationship is hypothesised to help with the development of viable preventative and treatment strategies.

Hyperbaric oxygen (HBO) treatment, a non-invasive method, has become a useful treatment for neurological disorders such dementia, traumatic brain injury, and cerebral ischemia [6–8]. Previous research has shown that breathing pure oxygen at pressures of more than one absolute atmospheric pressure (ATA) raises arterial and cerebral oxygen tension, which enhances oxygen delivery to the brain [9,10]. Numerous studies have shown that HBO treatment exerts positive therapeutic effects by modulating the release of inflammatory cytokines [11–13]. Although HBO has been shown to alleviate diminished blood flow, hypoxia, and neuroinflammation in the brain, its effect on dyslipidemia and neurodegeneration are not yet to be fully understood.

Apolipoprotein E (ApoE), predominantly expressed in astrocytes, controls phospholipid and cholesterol transport and redistribution within the central nervous system [14]. Hypercholesterolemia and atherosclerosis are observed in ApoE-deficient ($ApoE^{-/-}$) mice. Numerous investigations have demonstrated that hypercholesterolemia

exacerbates the accumulation of amyloid beta (Aβ) in the brain, resulting in neurodegenerative disorders and cognitive impairment [15,16]. Beyond this canonical role in cholesterol/lipid homeostasis, ApoE orchestrates multifaceted molecular mechanisms governing neurogenic processes, synaptic plasticity, neurite retraction, inflammatory cascades, tau hyperphosphorylation, and Aβ fibrillization. As a multifunctional glycoprotein it exhibits pleiotropic involvement in both neuroprotective pathways and neurodegenerative etiologies [17].

Currently, there are few lipid management interventions in the prevention and treatment of dementia and brain degeneration. Changes in lipid metabolism undoubtedly affect the microenvironment of brain tissue, although the precise role remains unknown. This study was aimed to assess the association between specific changes in lipid metabolism and lesions in brain tissue, excluding age-related variables, thereby contributing to the clinical management of dyslipidemia and brain degeneration.

2. Materials and Methods

2.1 Animal Subjects

All experimental procedures were approved by the Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University. Male ApoE$^{-/-}$ mice (C57BL/6J background) and wild-type (WT) C57BL/6J mice (eight months old) were obtained from Gempharmatech Co., Ltd. (Nanjing, Jiangsu, China). Animals were maintained under specific pathogen-free conditions with controlled 12-hour light/dark cycles.

2.2 Experimental Groups

Mice were stratified into three cohorts (n = 7 per group): WT group: Age-matched C57BL/6J mice serving as baseline controls, an ApoE$^{-/-}$group: Untreated ApoE$^{-/-}$ mice maintained on a standard diet and an ApoE$^{-/-}$ +HBO group: ApoE$^{-/-}$ mice subjected to HBO therapy for 10 consecutive days.

2.3 HBO Intervention Protocol

HBO treatment was conducted using a rodent-specific hyperbaric chamber (YC3200J-X, Yantai Haote Oxygen Corporation, Yantai, Shandong, China) following established methodologies [18]. Briefly, mice were acclimatized in the chamber and exposed to 100% oxygen at 2.5 ATA daily. Chamber pressure was incrementally elevated to 2.5 ATA over 15 minutes, maintained for 60 minutes, then gradually normalized to ambient pressure over 15 minutes. Control cohorts (WT and untreated ApoE$^{-/-}$ mice) underwent identical chamber conditions with compressed air (1 ATA) for 90 minutes to account for procedural variables.

2.4 Behavior Tests

2.4.1 Novel Object Recognition Test

A novel object recognition assay was performed as described [19] using a 50 $\times$ 50 $\times$ 50 cm^3 acrylic arena. Twenty-four hours prior to testing, mice underwent a five minute habituation phase in the empty arena. During training, two identical objects (A and B) were positioned equidistant from arena walls. Mice were placed facing away from objects and allowed five minutes for exploration. After a one hour retention interval, object B was replaced with novel object C for five minutes. A 24-hour post-training test phase introduced object D in place of C to assess discrimination. Sessions were video-recorded for offline analysis. Discrimination indices were calculated as [(T<novel object exploration> – T<familiar object exploration>) / (T<novel object exploration> + T<familiar object exploration>)] $\times$ 100, where T denotes exploration time.

2.4.2 Fear Conditioning Paradigm

Contextual fear conditioning was conducted per established protocols [20]. During training, mice were placed in a conditioning chamber for a three minute baseline period followed by three two second, 0.8-mA foot shocks delivered at one minute intervals. Subjects were returned to home cages 30 seconds post-stimulation. Memory retention was assessed one hour later via a three minute re-exposure to the unmodified chamber with freezing behavior quantification. A 24-hour post-training extinction test replicated this procedure without shocks, with freezing duration recorded using automated tracking software.

2.5 Tissue Processing and Specimen Collection

After termination of the experiment, cohort-matched mice were euthanized (gradual exposure to CO_2 (30% chamber volume displacement per minute) in a sealed chamber, followed by cervical dislocation to ensure death) following final body mass measurements. Blood samples were collected via retro-orbital venipuncture into anticoagulant-treated tubes. Cerebral tissues were divided for preservation: one hemisphere underwent fixation in 4% paraformaldehyde for histomorphometric analysis, while contralateral hemispheres were snap-frozen in liquid nitrogen and stored at –80 °C for molecular assays.

2.6 Serum Lipid Profiling

Collected blood samples were centrifuged at 3500 $\times$g (4 °C, 5 min) to isolate serum, which was aliquoted and cryopreserved at –80 °C until biochemical analysis. Lipid parameters: TC, TG, LDL-C, and HDL-C were quantified via enzymatic colorimetric assays using standardized commercial kits (A111-1-1 for TC, A110-1-1 for TG, A113-1-1 for LDL-C, and A112-1-1 for HDL-C, Jiancheng Bioengineering Institute, Nanjing, Jiangsu, China).

Table 1. Primers of RT-qPCR.

Gene symbol	Primer Sequence (5′→3′)
absent in melanoma 2 (*AIM2*)	F: GTCCTCAAGCTAAGCCTCAGA R: CACCGTGACAACAAGTGGAT
glyceraldehyde-3-phosphate dehydrogenase (*GAPDH*)	F: CAAAAGGGTCATCATCTCC R: CCCCAGCATCAAAGGTG
interleukin-1 beta (*IL-1*β)	F: TCATTGTGGCTGTGGAGAAG R: AGGCCACAGGTATTTTGTCG
interleukin-6 (*IL-6*)	F: ATCCAGTTGCCTTCTTGGGACTGA R: TAAGCCTCCGACTTGTGAAGTGGT
inducible nitric oxide synthase (*iNOS*)	F: CCAAGCCCTCACCTACTTCC R: CTCTGAGGGCTGACACAAGG
nucleotide-binding oligomerization domain-like receptor 1 (*NLRP1*)	F: GGTGGTGTGAAGATGTTGTGT R: TCCATGTTCATCGTAGGGACC
nucleotide-binding oligomerization domain-like receptor 3 (*NLRP3*)	F: ATCAACAGGCGAGACCTCTG R: GTCCTCCTGGCATACCATAGA
NLR Family CARD Domain Containing 4 (*NLRC4*)	F: TCAAAGGCGACTGGAAAGAAG R: CGCCACTCCTTGCAGAAAC
tumor necrosis factor-α (*TNF-*α)	F: CATCTTCTCAAAATTCGAGTGACAA R: TGGGAGTAGACAAGGTACAACCC

2.7 Oxidative Stress Biomarker Analysis

Serum concentrations of nitric oxide (NO) and malondialdehyde (MDA), alongside superoxide dismutase (SOD) enzymatic activity, were determined using species-specific Enzyme-Linked Immunosorbent Assay (ELISA) kits (A012-1-2 for NO, A003-1-2 for MDA, and A001-3-2 for SOD, Jiancheng Bioengineering Institute) following manufacturer protocols. Absorbance measurements were normalized to internal standards.

2.8 RNA Extraction and Quantitative Real-Time Polymerase Chain Reaction (PCR)

Total RNA was isolated from frozen cortical tissues using the RNeasy Mini Kit (R701, Vazyme Biotech, Nanjing, Jiangsu, China), with genomic DNA removal via on-column DNase digestion. cDNA synthesis employed 1 µg RNA template processed with the HiScript III Reverse Transcriptase system (R223, Vazyme Biotech). Quantitative PCR amplification was performed using the AceQ SYBR Green Master Mix (Q131, Vazyme Biotech) on a QuantStudio 6 Flex system (4485697, Thermo Fisher Scientific, Woodlands, Singapore). Relative gene expression was normalized to Gapdh and calculated via the $2^{-\Delta\Delta Ct}$ method. The sequences of the primers are listed in Table 1.

2.9 Nissl Histochemistry

Tissue sections underwent sequential xylene immersion for deparaffinization followed by graded ethanol rehydration (100%, 95%, 70%, E111992, Aladdin Chemistry Co., Ltd., Shanghai, China). After distilled water rinsing, slides were stained with 1% toluidine blue (pH 4.5, T492282, Aladdin Chemistry Co., Ltd.) for 10 minutes at 25 °C. Sections were dehydrated through ascending ethanol series, cleared in xylene, and mounted with synthetic resin for bright-field microscopy (FV3000, Olympus, Tokyo, Japan). Cell layer thickness quantification were performed in three matched layer (cornu ammonis area (CA)1, CA3, dentate gyrus (DG)) per animal by ImageJ software (v1.53t, Research Services Branch, National Institute of Mental Health, Bethesda, MD, USA) with 10 equidistant sampling points per section.

2.10 Immunohistochemical Analysis

Antigen retrieval and staining protocols followed established methodology [21,22]. Sections were probed with rabbit polyclonal anti-Amyloid-β40 antibodies (1:200, GB14006-50, Servicebio Technology, Wuhan, Hubei, China) overnight at 4 °C. After PBS washes, biotin-conjugated goat anti-rabbit IgG secondary antibodies (1:500, SP-9003, ZhongShan Biotechnology, Beijing, China) were applied for one hour at 37 °C. Diaminobenzidine chromogen (S0101, ZhongShan Biotechnology) was utilized for signal development, followed by hematoxylin (E774767, Aladdin Chemistry Co., Ltd.) counterstaining, ethanol dehydration, and permanent mounting. Observation under a microscope and quantification of Aβ positive expression using ImageJ software.

2.11 ELISA

The concentration of IL-6 and TNF-α in the serum was measured by mouse ELISA Kit (EK206EGA-96, MultiSciences Biotech Co., Ltd., Hangzhou, Zhejiang, China) according to the manufacturer's instructions.

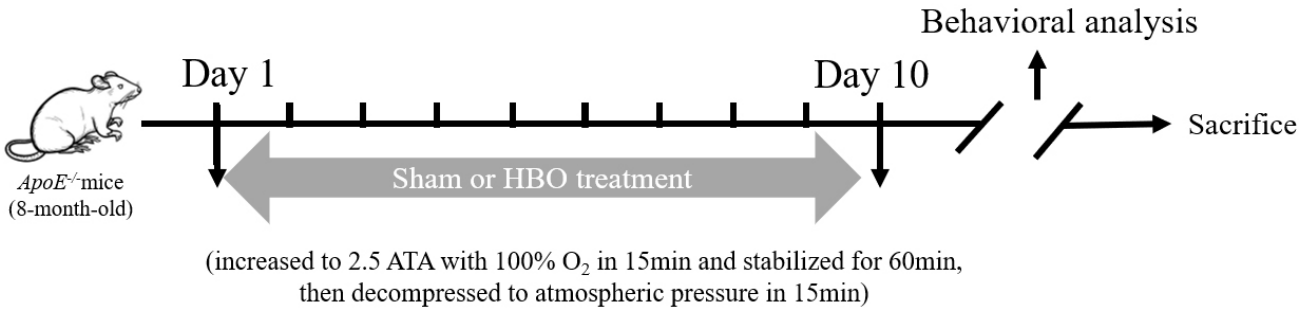

Fig. 1. Schematic illustration of the overall experimental procedure. A series of behavioral tests were performed after hyperbaric oxygen (HBO) treatment to assess cognitive function, including novel object recognition experiment and fear conditioning test. ATA, absolute atmospheric pressure; APOE$^{-/-}$, apolipoprotein E-deficient.

Table 2. Effect of HBO treatment on body weight and lipid levels in serum.

Metabolic parameters	Groups		
	WT	APOE$^{-/-}$	APOE$^{-/-}$+HBO
Body weight (g)	32.63 ± 0.32	35.32 ± 0.38***	32.42 ± 0.62$^{\#\#\#}$
TC (mmol/L)	2.79 ± 0.48	4.32 ± 0.28**	2.23 ± 0.4$^{\#\#\#}$
TG (mmol/L)	0.97 ± 0.13	3.56 ± 0.21***	1.7 ± 0.43*$^{\#\#\#}$
LDL-C (mmol/L)	0.52 ± 0.07	10.88 ± 0.45***	6.33 ± 0.47***$^{\#\#\#}$
HDL-C (mmol/L)	2.73 ± 0.18	0.72 ± 0.03***	0.67 ± 0.07***

Values represent mean ± SD for body weight and Lipid parameters of 6 animals in each group. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$ vs. WT mice, $^{\#\#\#}$ $p < 0.001$ vs. APOE$^{-/-}$ mice without HBO treatment. WT, wild-type group; APOE$^{-/-}$, apolipoprotein E-knockout mice group; APOE$^{-/-}$+HBO, APOE$^{-/-}$ mice, that received hyperbaric oxygen treatment; TC, total cholesterol; TG, tri-glyceride; LDL-C, low density lipoprotein cholesterol; HDL-C, high density lipoprotein cholesterol.

2.12 Statistical Evaluation

All datasets are expressed as mean ± standard deviation. Intergroup comparisons were performed by one-way analysis of variance (ANOVA) with Tukey's multiple comparisons test using GraphPad Prism 8.0.2 (GraphPad Software, La Jolla, CA, USA). Statistical significance was defined as $p < 0.05$.

3. Results

3.1 Effect of HBO Treatment on Cognitive Functions in APOE$^{-/-}$ Mice

The overall experimental procedure is illustrated in Fig. 1. To evaluate the effect of HBO treatment on cognitive function, both novel object recognition and fear conditioning assays were performed. In the novel object recognition experiment, the discrimination indices of mice in the WT, ApoE$^{-/-}$ and ApoE$^{-/-}$+HBO groups were 0.45 ± 0.15, 0.17 ± 0.04 and 0.34 ± 0.11 respectively and revealed that ApoE$^{-/-}$ mice were significantly more interested in new objects following HBO treatment (Fig. 2A,B, one-way ANOVA: F (2,15) = 9.977, $p = 0.0018$). During the test of contextual fear conditioning, it was found that mice in the ApoE$^{-/-}$ group showed decreased freezing times when compared with those of the WT group, while those of the ApoE$^{-/-}$+HBO group showed increased freezing times, suggesting that HBO treatment promotes recognition memory process in ApoE$^{-/-}$ mice (Fig. 2C,D, one-way ANOVA: F (2,15) = 10.77, $p = 0.0013$). Thus, these data provide compelling evidence that HBO treatment significantly reduced learning and memory deficits induced by dyslipidemia.

3.2 Effect of HBO Treatment on Body Weight and Lipid Levels in Serum

When compared with WT mice, ApoE$^{-/-}$ mice exhibited a phenotype of abnormal lipid metabolism, characterized by elevated levels of TC, TG, LDL-C and decreased levels of HDL-C, but after the HBO treatment, the body weights, TC, TG, and LDL-C level were significantly reduced (one-way ANOVA: $p < 0.05$, Table 2). However, HBO treatment did not affect serum HDL-C concentrations of the ApoE$^{-/-}$ mice. It is of interest to note that HBO treatment significantly reduced body weight and TC levels in ApoE$^{-/-}$ mice, making them similar to those of the WT mice.

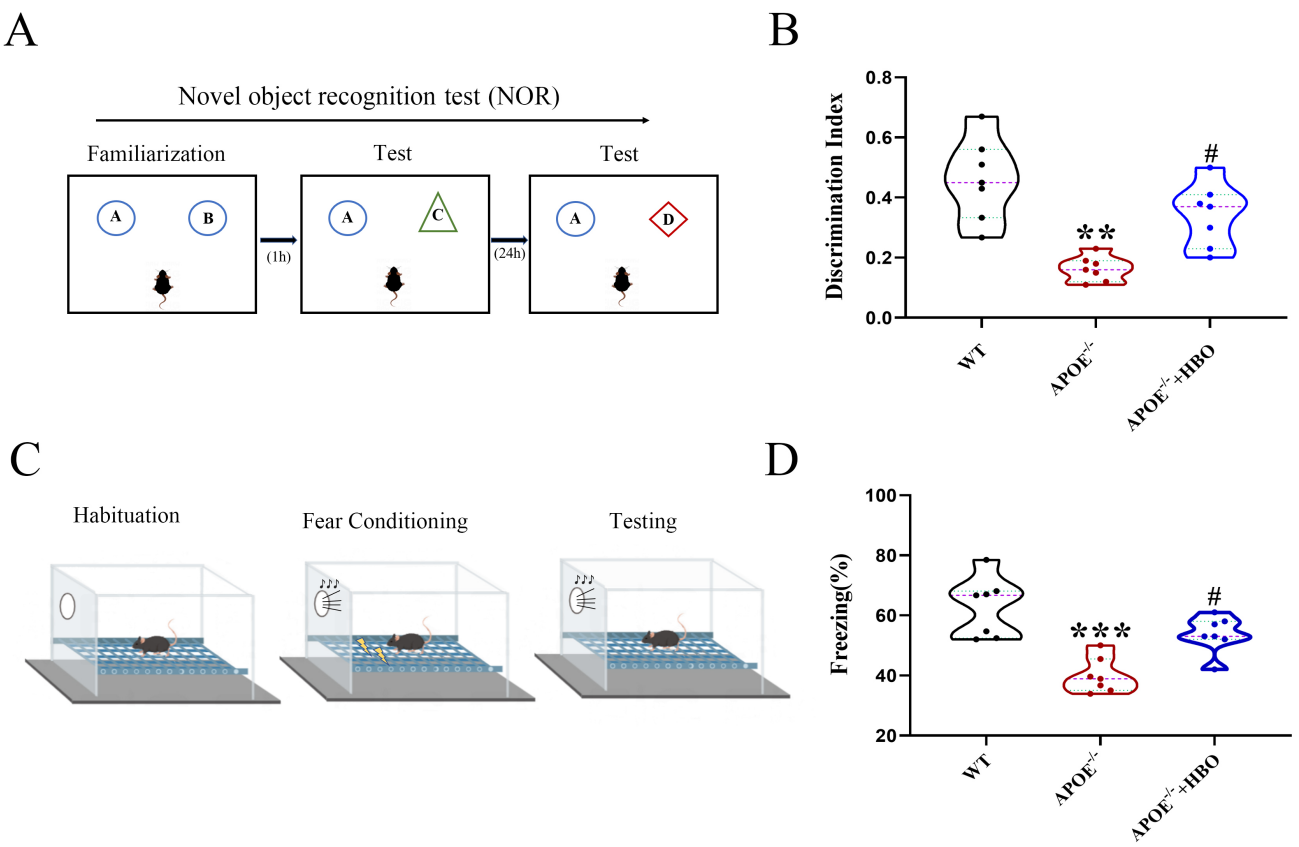

Fig. 2. Effect of HBO treatment on cognitive function and behaviors of mice. NOR experiment (A) and Fear conditioning test (C) were performed to assess the mice behavior. (B) Discrimination index of each group. (D) The freezing response. All data represent mean ± SD, ** $p < 0.01$, *** $p < 0.001$ vs. WT mice, $^{\#}$ $p < 0.05$ vs. APOE$^{-/-}$ mice without HBO treatment. n = 7 in each group.

3.3 Effect of HBO Treatment on the Structure of the Hippocampus in ApoE$^{-/-}$ Mice

Changes in hippocampal structure are associated with memory impairment and cognitive dysfunction [22–24]. Pyramidal cells in the hippocampal region of the WT control mice had regular and orderly arrangements, full structures, uniform chromatin distribution, round and sizable nuclei, and transparent cytoplasm and nucleoli, as demonstrated by Nissl staining. Conversely, neurons in the hippocampus of mice in the ApoE$^{-/-}$ group's were organized loosely and erratically, with some of them exhibiting noticeable shrinkage in addition to having darkly pigmented, condensed nuclei (Fig. 3). When compared with the WT group, the thickness of the cell layer in the CA3 area of the ApoE$^{-/-}$ mice decreased significantly. As shown in Fig. 3, HBO treatment partially reversed the neuronal morphological alterations seen in the ApoE$^{-/-}$ group, in particular the increased thickness of the cell layer in the CA3 area. Similar trends were observed in the other subregions CA1 and DG as well.

3.4 Effect of HBO Treatment on the Level of Aβ in the Hippocampus of the ApoE$^{-/-}$ Mice

As one of the main components of neuronal cell membranes, lipids are intimately linked to the balance between normal metabolism and abnormal accumulation of Aβ [25, 26]. The expression level of Aβ in the model mouse hippocampi was determined by immunohistochemical staining. According to the findings in Fig. 4, intra-neuronal Aβ was more abundant in the hippocampus of ApoE$^{-/-}$ mice than that in the WT group. Aggregation of Aβ peptide is the main cause of neuronal damage in Alzheimer's disease (AD) [27]. However, HBO treatment induced a reduction in neuronal damage resulting from Aβ, which is thought to improve the intracerebral microenvironment in ApoE$^{-/-}$mice. Thus, HBO treatment may exert great therapeutic potential for AD.

3.5 Effect of HBO Treatment on Oxidative Stress in ApoE$^{-/-}$Mice

To determine changes in oxidative damage after HBO treatment in ApoE$^{-/-}$ mice, SOD activities, MDA, and NO concentrations were measured (Table 3). As compared with the WT group, ApoE$^{-/-}$ mice displayed significantly lower SOD activities (38% of WT), and elevated MDA con-

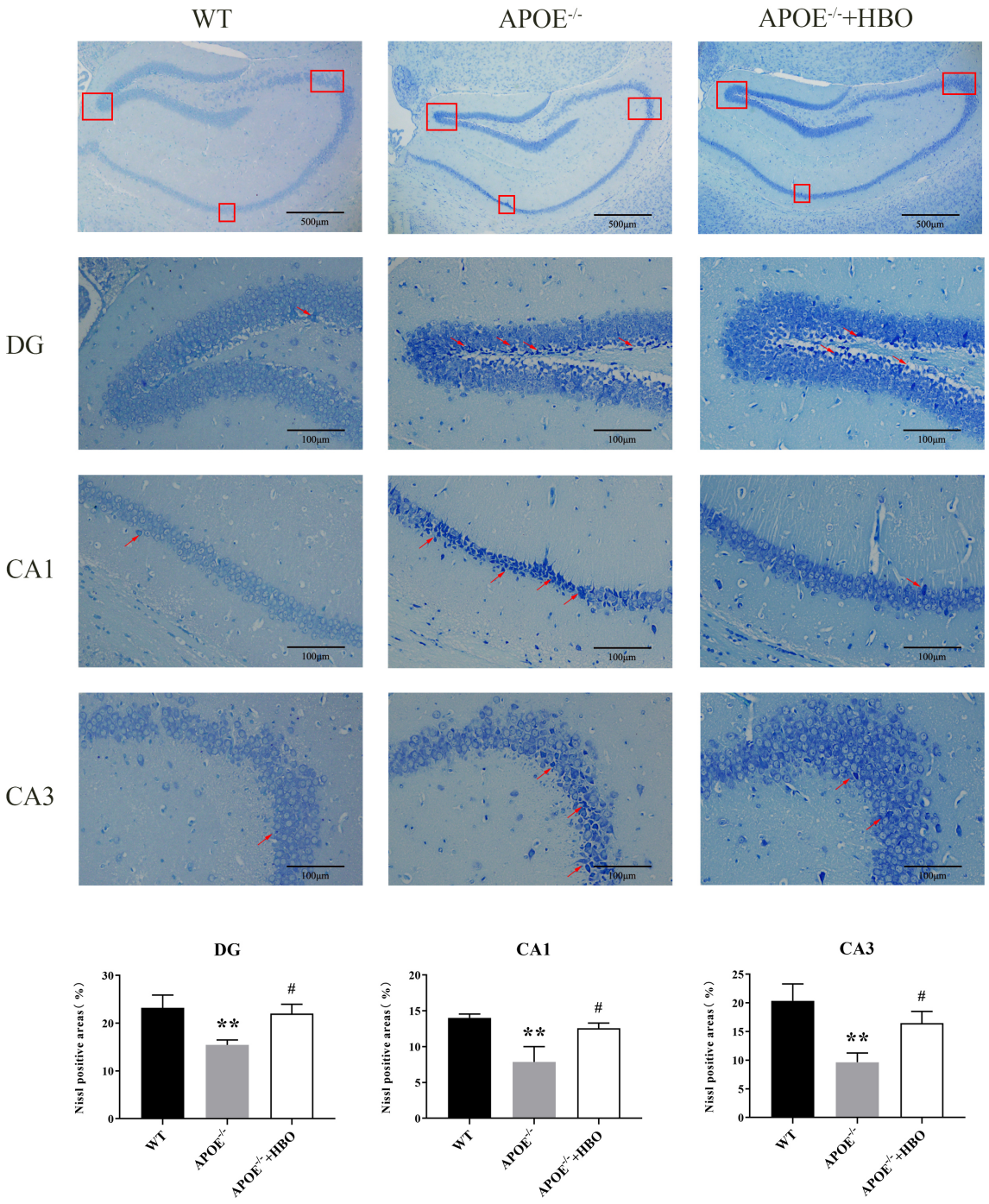

Fig. 3. Effect of HBO treatment on hippocampal damage. Hippocampal morphology with Nissl staining. The scale bar = 500 μm (the top panels), 100 μm (the middle panels). n = 4 in each group. The top of the image is the representative immunoblots and the bottom of the image is the quantification for analysis. The red boxes indicates different regions of the hippocampus that have been selected for analysis. In neuroanatomy, the hippocampus is often divided into subregions (e.g., CA1, CA3, or dentate gyrus), and the box highlights these areas. The red arrow shows the Nissl body. The changes in Nissl bodies can signal apoptosis or neurodegeneration. The arrow directs attention to these features. ** $p < 0.01$ vs. WT mice, $^{\#}$ $p < 0.05$ vs. APOE$^{-/-}$ mice without HBO treatment. CA, cornu ammonis area; DG, dentate gyrus.

centration. Interestingly, the HBO treatment reversed the alterations of SOD and MDA in ApoE$^{-/-}$ mice (one-way ANOVA: $p < 0.05$, with data meeting normality and equal variance assumptions), with little effect on NO concentration. These results indicate that HBO treatment has an antioxidative stress effect and may alleviate oxidative damage in ApoE$^{-/-}$ mice.

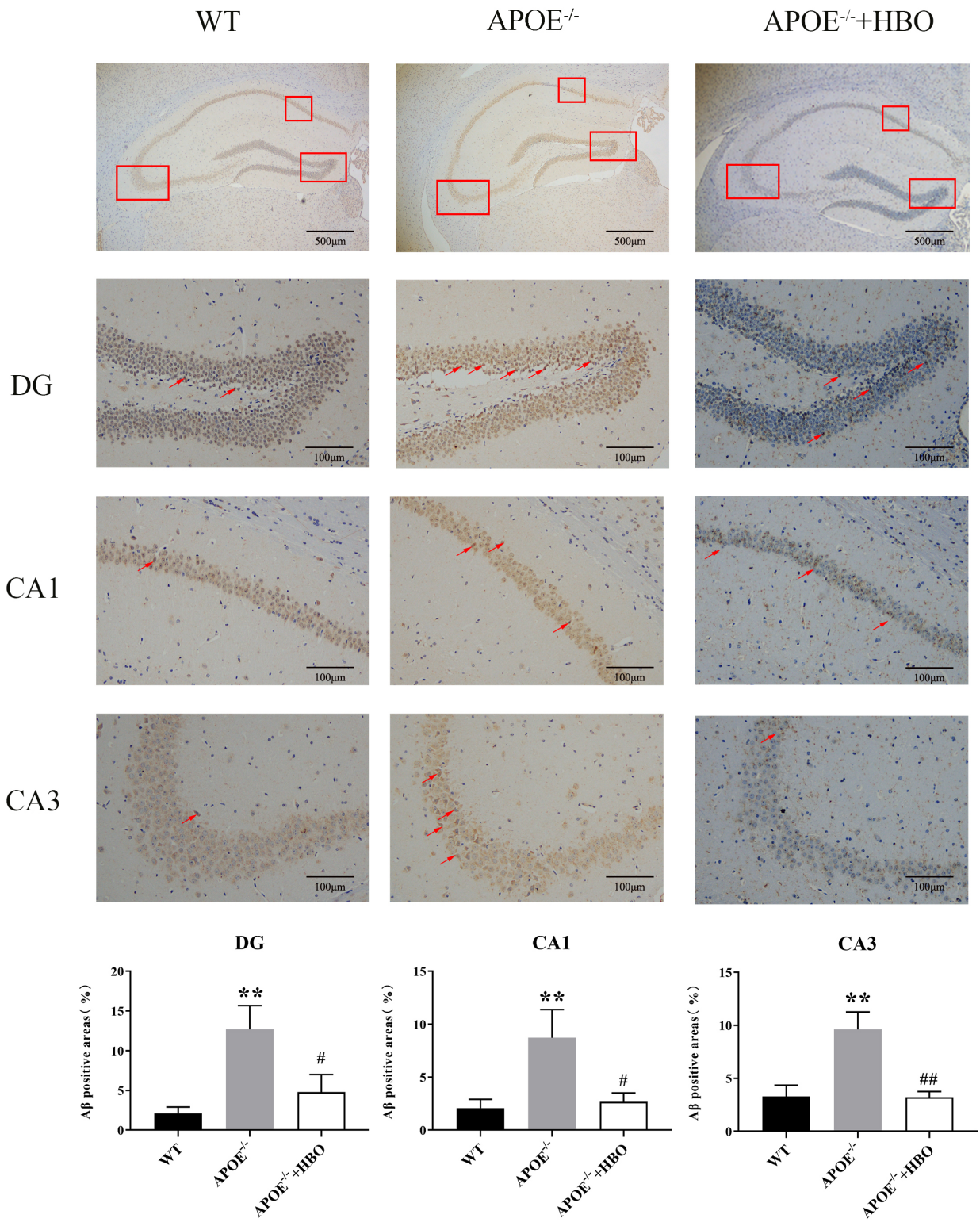

Fig. 4. Effect of HBO treatment on amyloid plaque burden in the hippocampus level of Aβ. Immunohistochemistry was used to conduct histopathological analysis of brain sections. Cytoplasmic yellow/brown cytoplasm was observed in the hippocampus. WT, wild-type group; APOE$^{-/-}$, apolipoprotein E-knockout mice group; APOE$^{-/-}$+HBO, APOE$^{-/-}$ mice, that received hyperbaric oxygen treatment; n = 4 in each group. The red boxes indicates different regions of the hippocampus that have been selected for analysis (e.g., CA1, CA3, and DG). The red arrow shows Aβ-positive cells. The scale bar = 500 μm (the top panels), 100 μm (the middle panels). The top of the image is the representative immunoblots and the bottom of the image is the quantification for analysis of the expression of Aβ. ** $p < 0.01$ vs. WT mice, $^{\#}$ $p < 0.05$, $^{\#\#}$ $p < 0.01$ vs. APOE$^{-/-}$ mice without HBO treatment.

Table 3. Effect of HBO treatment on oxidative stress.

Biomarkers of oxidative stress	Groups		
	WT	APOE$^{-/-}$	APOE$^{-/-}$+HBO
SOD activity (U/mL)	11.0 ± 1.9	4.2 ± 2.4*	12.4 ± 3.0$^{\#}$
MDAconcentration (nmol/mL)	32.1 ± 12.9	43.5 ± 6.9	14.5 ± 8.6*$^{\#\#\#}$
NO concentration (μmol/L)	0.008 ± 0.013	0.072 ± 0.002***	0.067 ± 0.001***

Values represent mean ± SD for serum SOD activities and MDA, NO concentrations in each group, n = 7. * $p < 0.05$, *** $p < 0.001$ vs. WT mice, $^{\#}$ $p < 0.05$, $^{\#\#\#}$ $p < 0.001$ vs. APOE$^{-/-}$ mice without HBO treatment. SOD, superoxide dismutase; MDA, malondialdehyde; NO, nitric oxide.

3.6 Effect of HBO Treatment on the Inflammatory Response in ApoE$^{-/-}$ Mice

The mRNA expression of inflammatory factors such as *IL-1β*, *IL-6*, *TNF-α* and inducible nitric oxide synthase (*iNOS*) were measured to investigate if HBO treatment affects the inflammatory response. Elevated expression levels of pro-inflammatory factors were found in the ApoE$^{-/-}$ mice group (one-way ANOVA: $p < 0.05$). As shown in Fig. 5, the expression levels of *IL-1β*, *IL-6* and *iNOS* were significantly reduced after the HBO treatment. Although *TNF-α* expression was not significantly different (see Fig. 5C), there was still a downward trend. Furthermore, an apparent increase in IL-6 and TNF-α was detected in the serum of ApoE$^{-/-}$ mice compared to WT mice (see Fig. 5E,F). Meanwhile, HBO treatment decreased the above inflammation. Previous studies have suggested that the inflammasome plays a crucial role in pathogen recognition and the innate immune response [29,30]. The expression of several inflammasome components were determined by real-time PCR, including the NOD-like receptor (NLR) family pyrin domain containing 1 (*NLRP1*), *NLRP3*, CARD-domain containing 4 (*NLRC4*), as well as absent in melanoma 2 (*AIM2*). The mRNA expression of the inflammasome components in the ApoE$^{-/-}$ mice group was significantly higher than that of the controls (one-way ANOVA: $p < 0.05$, Fig. 5G–J). After the HBO treatment, the expression of these inflammasome components were significantly reduced (one-way ANOVA: $p < 0.05$, Fig. 5G–J). These findings suggest that abnormal lipid metabolism exacerbates the inflammatory response, and HBO treatment significantly reduces inflammation-activating responses *in vivo*.

4. Discussion

Dyslipidemia and obesity are the main risk factors for coronary heart disease, hypertension, and stroke, posing a serious threat to human health. As a result, the treatment of dyslipidemia has attracted widespread attention. HBO treatment has been approved by the FDA for many disorders [28,31], and recently its potential benefits in treating other pathological diseases has also been studied, including traumatic brain injury, spinal cord injury, and stroke [32–35]. In this study, the effects of HBO treatment on cognitive function, lipid metabolism, amyloid deposition, neuroinflammation, and other pathologies were investigated in an ApoE$^{-/-}$ model. Results revealed that HBO treatment improves cognitive function, and lipid metabolism levels, reduces neuronal damage and Aβ aggregation, and attenuates neuroinflammation and oxidative stress. These changes were accompanied by a reduction in pro-inflammatory cytokines and alterations in oxidative stress-related factors in ApoE$^{-/-}$ mice.

Consistent with previous results [36], the experiment reported here showed that ApoE$^{-/-}$ mice exhibit increase body weight and elevated serum levels of TC, LDL-C and TG. These findings confirm that ApoE deletion enhances lipoprotein degradation and indicate that the model used here was successful. Results showed that HBO treatment significantly reduced TG, TC, HDL-C and body weight levels in ApoE$^{-/-}$ mice, which is consistent with previous findings [37]. These changes in lipid profile suggest that HBO treatment may significantly improve lipid metabolism and effectively reduce the risk of dyslipidemia. Further research is needed to clarify which lipoproteins play a key role in the process.

Given that lipids are a significant component of the cell bilayer membrane, play a crucial role in both the normal physiological function of neurons and the structural development of the brain [38], dysregulated lipid homeostasis has been related to the pathological progression of various neurodegenerative diseases [39,40]. Increasingly, studies have focused on the relationship between hyperlipidemia and neuropathy [40,41]. For example, a Spanish cohort study found that patients with familial hypercholesterolemia had a significantly higher incidence of mild cognitive impairment than those without that condition [42], while a 21 year follow-up cohort study in Finland showed that middle-aged individuals with higher serum TC have a higher risk of developing dementia or AD in the future [43]. Hypercholesterolemia has been shown to accelerate the accumulation of Aβ oligomers inside neurons and the subsequent loss of synapses, which causes memory impairment in a transgenic mouse model of AD [44]. Cholesterol and ApoE are implicated in fibrillar plaque formation or maintenance in the transgenic mouse model of AD-type amy-

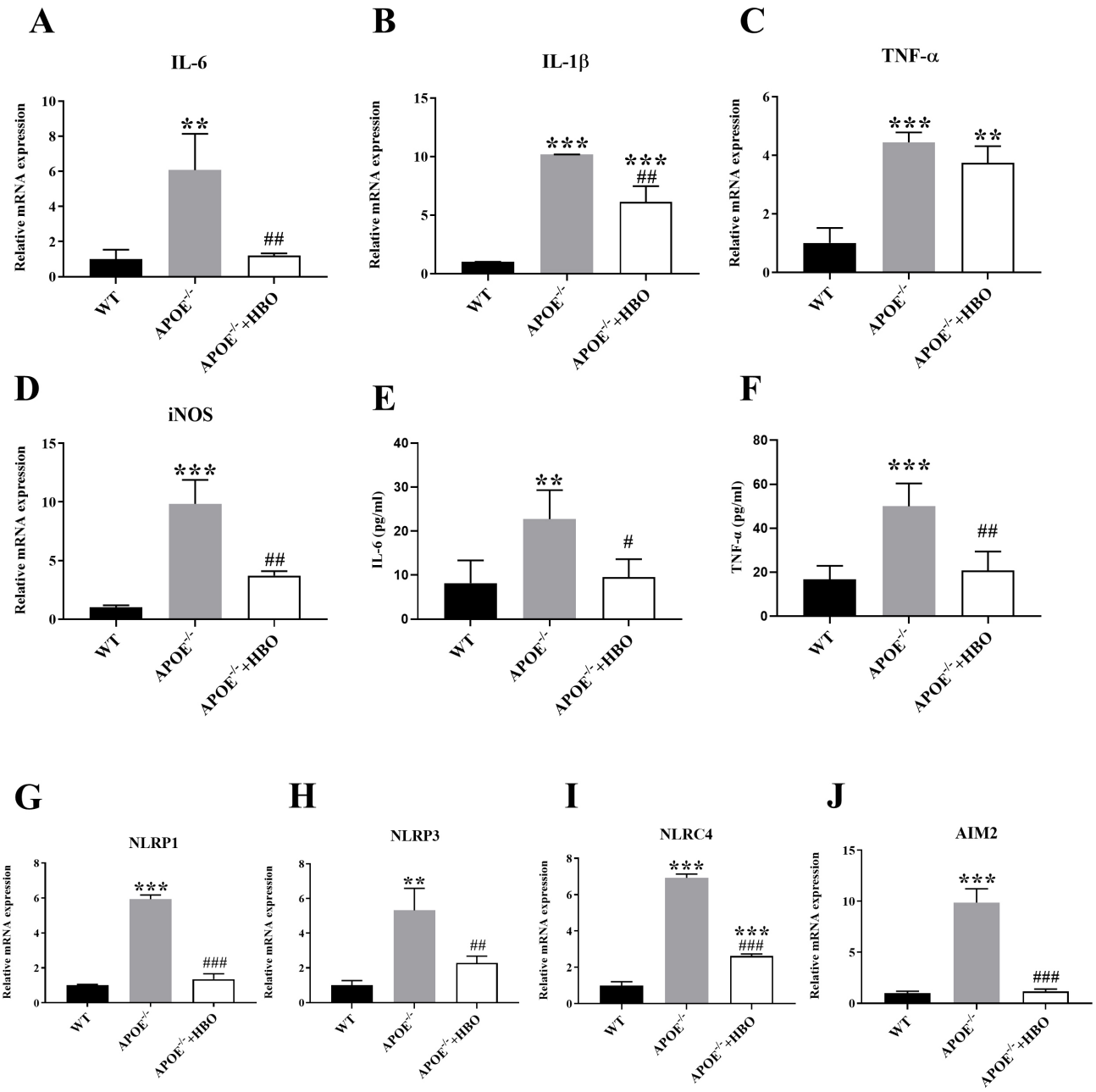

Fig. 5. Effect of HBO treatment on systemic inflammatory response. (A–D) Quantitative mRNA expressions of inflammation cytokine, *IL-1β*, *IL-6*, *TNF-α* and *iNOS*. (E,F) The secretion of IL-6*β* and TNF-*α* from serum were detected by ELISA. (G–J) Quantitative mRNA expressions of inflammasome components, *NLRP1*, *NLRP3*, *NLRC4*, and *AIM2*. Data are represented as mean ± SD of three independent experiments in duplicates. WT, wild-type group; $APOE^{-/-}$, apolipoprotein E-knockout mice group; $APOE^{-/-}$+HBO, $APOE^{-/-}$ mice, that received hyperbaric oxygen treatment. ** $p < 0.01$, *** $p < 0.001$ vs. WT mice, $^{\#}$ $p < 0.05$, $^{\#\#}$ $p < 0.01$, $^{\#\#\#}$ $p < 0.001$ vs. $APOE^{-/-}$ mice without HBO treatment. n = 3 in each group.

loidosis [45]. Additionally, oxygen supplementation improves cognitive function and increase the expression of proteins involved in A*β* clearance in the eye lenses of 3xTg mice [46]. When compared to ordinary oxygen supplementation, HBO treatment promotes tissue oxygenation more effectively. Based on such findings, it is hypothesized that HBO treatment improves cognitive deficit, regulates lipid metabolism and reduces A*β* accumulation, ultimately improving neurological function. Indeed, the results reported here show that HBO treatment improves cognitive function, reduces neuronal damage and improves A*β* clearance, suggesting that it improves brain function while regulating hyperlipidemia.

Oxidative stress and inflammatory response are crucial in the development of dyslipidemia and related diseases, such as neurological diseases [47]. Under normal

conditions, the body has certain levels of antioxidant enzymes that remove excess oxygen radicals in a timely manner and maintain homeostasis. SOD, the main antioxidant enzyme, contributes to a large accumulation of oxygen radicals when its activity decreases. As another significant indicator of antioxidant capacity, MDA serves as an indirect indicator of the extent of tissue peroxidation damage and the rate and degree of lipid peroxidation inside the body [48]. Chen *et al.* [49] documented that in a mouse aging model induced by D-galactose, HBO prevents cognitive impairments by reducing oxidative damage and suppressing inflammatory responses. In the present study, we show that HBO treatment can significantly improve oxidative damage by reducing the serum levels of MDA and increasing SOD activities in ApoE$^{-/-}$ mice. This indicates that HBO treatment improves dyslipidemia and associated problems may be through the suppression of oxygen-free radicals.

Lipid deposition promotes inflammation. The sustained excessive release of pro-inflammatory factors, such as TNF-α, IL-1β, and IL-6, leads to the gradual activation of an inflammatory cascade. Systemic inflammation has been shown to cause a neuroinflammatory response, which is characterized by persistent microglial activation and has been shown to have negative effects on learning and memory in both human patients [50,51] and rodent models [52]. Dempsey *et al.* [53] reported that inhibiting the NLRP3 inflammasome promoted Aβ clearance and improved cognitive performance. The findings reported here indicate that HBO treatment successfully prevented inflammasome activation and decreased the accumulation of Aβ in the brains of ApoE$^{-/-}$mice. Moreover, HBO-treated ApoE$^{-/-}$ mice showed decreased expression of serum pro-inflammatory factors. Therefore, HBO is an efficacious treatment that exerts a clear protective effect by inhibiting inflammatory response.

Following decades of clinical validation, HBO has solidified its role as a versatile and safe intervention across diverse medical disciplines. In recent years, its application has expanded into neuroscience, where it has shown therapeutic potential as a neuromodulation strategy for neurological and psychiatric disorders. Although preclinical and clinical studies have confirmed its neuroprotective benefits, the molecular mechanisms underlying these effects are not yet fully understood [8–10]. Our future investigation will employ RNA sequencing to map transcriptomic signatures to uncover conserved regulatory pathways and candidate molecular targets for cognitive enhancement. A limitation of our study is that we did not administer HBO to different types of animals in various forms, nor to a small group of humans with specific risk factors. As a result, we were unable to fully separate the effects of HBO on cognition from potential confounding factors. Throughout the treatment process, the medical staff should closely monitor the patient's vital signs in order to respond promptly to any potential emergencies.

Given the urgency of dementia prevention, particularly among middle-aged individuals with genetic risk factors (e.g., APOE4 carriers), a family history of dementia, dyslipidaemia, or prodromal cognitive decline, we emphasize the importance of bidirectional translational research. Careful consideration is essential when translating these findings into clinical practice, and identifying the optimal treatment regimen will be a challenging task. Insights derived from preclinical models must undergo rigorous validation through stratified clinical trials to refine patient selection and treatment protocols [13,54]. Furthermore, we need to further explore whether it is appropriate to prescribe an individualized treatment regimen for each patient.

5. Conclusions

Evidence indicates that HBO treatment is evolving from an adjunctive emergency intervention into a promising protective pharmacological strategy. While current research demonstrates HBO's capacity to reduce oxidative stress and inflammatory responses, it is crucial to emphasize that causality has not yet been directly established. As this study primarily used mouse models, further clinical validation of these findings remains essential. This limitation may partially compromise the comprehensiveness of the reported outcomes. Continued investigation into HBO's molecular mechanisms and novel therapeutic applications will advance its integration into clinical practice. To effectively translate HBO's benefits into clinical settings (akin to "preventive strategies"), it is imperative to carefully assess patient-specific risk factors, comorbidities, and potential drug interactions that impact HBO-related protection.

Availability of Data and Materials

The data in this study are available from the corresponding author upon request.

Author Contributions

GYD and YXL conducted the majority of the experimental procedures. LXW and XC contributed to conceptualize and supervise the study. HJL was responsible for data collection and compilation. CQ analyzed the data and performed a statistical analysis. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

The Institutional Animal Care and Use Committee (IACUC) of Nanjing Medical University approved all animal procedures used in this study (Ethic Approval Number: 2008067). The animal procedures were performed in strict accordance with the guideline of the Institutional Animal Care and Use Committee of Nanjing Medical University.

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Conflict of Interest

The authors declare no conflict of interest.

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