INTRODUCTION

Alzheimer’s disease (AD) is a neurodegenerative disorder characterized by progressive learning and memory deficits. Although the pathogenesis of AD is not well understood, it is widely accepted that AD is associated with plaques and tangles within the brain and that the plaques distributed throughout the cortex and hippocampus are mostly insoluble deposits of amyloid β peptide (Aβ). The accumulation of Aβ in patients with AD can activate astrocytes and induce the generation of proinflammatory cytokines released by activated astrocytes, leading to brain damage and cognitive decline. Additionally, higher numbers of astrocytes have been found to surround Aβ deposits in patients with AD, compared to those without. Activated astrocytes also contribute to the accumulation of Aβ by secreting inflammatory proteins.

The molecular mechanisms involved in neuronal damage, astrocyte activation, and cognitive decline associated with Aβ accumulation in patients with AD have not yet been fully elucidated. Recent studies have highlighted an important role for p38 mitogen-activated protein kinase (MAPK) signal pathway as a potential target for treatment in AD. The phosphorylation of p38 MAPK regulates neuroinflammation, cyto-

Hyperbaric Oxygen Pretreatment Improves Cognition and Reduces Hippocampal Damage Via p38 Mitogen-Activated Protein Kinase in a Rat Model

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Purpose: To investigate the effects of hyperbaric oxygen (HBO) pretreatment on cognitive decline and neuronal damage in an Alzheimer’s disease (AD) rat model.

Materials and Methods: Rats were divided into three groups: normal saline (NS), AD, and HBO+AD. In the AD group, amyloid β peptide (Aβ)1-40 was injected into the hippocampal CA1 region of the brain. NS rats received NS injection. In the HBO+AD group, rats received 5 days of daily HBO therapy following Aβ1-40 injection. Learning and memory capabilities were examined using the Morris water maze task. Neuronal damage and astrocyte activation were evaluated by hematoxylin-eosin staining and immunohistochemistry, respectively. Dendritic spine density was determined by Golgi-Cox staining. Tumor necrosis factor-α, interleukin-1β, and interleukin-10 production was assessed by enzyme-linked immunosorbent assay. Neuron apoptosis was evaluated by terminal deoxynucleotidyl transferase dUTP nick end labeling. Protein expression was examined by western blotting.

Results: Learning and memory dysfunction was ameliorated in the HBO+AD group, as shown by significantly lower swimming distances and escape latency, compared to the AD group. Lower rates of neuronal damage, astrocyte activation, dendritic spine loss, and hippocampal neuron apoptosis were seen in the HBO+AD than in the AD group. A lower rate of hippocampal p38 mitogen-activated protein kinase (MAPK) phosphorylation was observed in the HBO+AD than in the AD group.

Conclusion: HBO pretreatment improves cognition and reduces hippocampal damage via p38 MAPK in AD rats.

Key Words: Hyperbaric oxygen, astrocytes, TNF-α, cognitive dysfunction, p38 MAPK
skeletal remodeling, and tau hyperphosphorylation, contributing to aggravation of AD.\(^7\)

Hyperbaric oxygen (HBO) treatment exhibits neuroprotective effects. HBO therapy reportedly provided neuroprotection in a rat model of spinal cord injury.\(^8\) Moreover, HBO reduced the severity of brain injury and ameliorated behavioral function in a rat model of neonatal hypoxia-ischemia.\(^9\) HBO treatment also reportedly alleviates chronic constrictive injury-induced neuropathic pain and inhibits endoneuronal tumor necrosis factor-\(\alpha\) (TNF-\(\alpha\)) production\(^,\)\(^10\) suggesting that HBO therapy has anti-inflammatory effects. The antioxidant effects yielded by HBO improve the learning and memory impairments in AD rats. HBO exerts potential protective effects through inhibiting mitochondria-dependent apoptosis induced by A\(\beta\)-mediated oxidative stress.\(^11\) A\(\beta\) causes a significant decrease in the memory and learning capabilities of rats, accompanied by neuronal damage in the hippocampus, as well as the overproduction of methane dicarboxylic aldehyde and NO. HBO efficiently improves memory and learning ability possibly via reducing hippocampal neuron injury and enhancing the activities of oxidative scavenging enzymes.\(^12\) Thus, the use of HBO may be a promising therapeutic option for the management of AD. Nevertheless, the precise effects of HBO on the development of A\(\beta\) accumulation-induced cognitive deficits and the mechanisms of these effects remain unclear.

In the present study, we investigated the protective effects of HBO pretreatment on learning and memory dysfunction, neuronal damage, and astrocyte activation in a rat model of AD. The underlying mechanisms were also elucidated. Our findings provide valuable insights into understanding the pathogenesis of AD, as well as promising approaches to the management of cognitive decline in patients with AD.

**MATERIALS AND METHODS**

**Animals**

Twenty-four 4-month-old male Sprague-Dawley rats weighing 260 to 290 g were obtained from the Center of Laboratory Animal Science of GuangDong (SCXK 2013-0002). The Animal Ethics Committee of Guangzhou Women and Children’s Medical Center (Guangzhou, China) approved all of the experimental protocols. All experiments were performed in accordance with the Guidelines for the Care and Use of Laboratory Animals of the National Institutes of Health and the Animal Welfare Act.

**Experimental assignments and model establishment**

The rats were randomly divided into three groups of eight rats each using a random number table. The three groups were the normal saline control (NS group), AD group, and AD+HBO group. A rat model of AD was established as follows. The rats were anesthetized and placed on a stereotaxic apparatus (I-C type; RWD Life Science Co. Ltd., Shenzhen, China). A\(\beta\)\(_{1-40}\) was injected into the hippocampal CA1 region: 3.2 mm posterior to the bregma, 2.0 mm lateral to the midline, and 2.9 mm ventral to the surface of the skull. A hole was drilled in the parietal skull plate to expose the dura mater. A micro sample syringe (SR034 Shanghai Laser Co. Ltd., Shanghai, China) preloaded with 2 \(\mu\)L of A\(\beta\)\(_{1-40}\) (5 \(\mu\)g/\(\mu\)L, Sigma-Aldrich, St. Louis, MO, USA) was slowly inserted into the bilateral hippocampal CA1 region through the opening in the skull. Prior to use, A\(\beta\)\(_{1-40}\) was dissolved in distilled water to a working concentration of 5 \(\mu\)g/\(\mu\)L and incubated at 37°C for 1 week to form A\(\beta\) oligomers. Rats in the AD and AD+HBO groups received injections of A\(\beta\)\(_{1-40}\). Rats in the NS group underwent identical procedures but were injected with 2 \(\mu\)L of NS instead of A\(\beta\)\(_{1-40}\).

**HBO therapy**

HBO therapy was conducted as previously described.\(^13\) The chamber was filled with pure oxygen for 10 min. Rats in the AD+HBO group were placed into the chamber for HBO therapy. The chamber was compressed at a consistent compression rate of 10 kPa/min to a target pressure of 2.0 atmospheres absolute pressure, and this target pressure was maintained for 60 min. The chamber was then decompressed at a consistent compression rate of 10 kPa/min to normal atmospheric pressure. The entire procedure lasted for 100 min. Rats in the AD+HBO group received HBO therapy once daily following surgery. The HBO treatment began on the first postoperative day and ended on the fifth postoperative day. Rats in the NS and AD groups were simply placed into the chamber for approximately 100 min without compression or decompression treatment.

**Morris water maze test**

The Morris water maze task was used to assess spatial learning and memory ability in the rats. The Morris water maze apparatus was provided by the Institute of Materia Medica, Chinese Academy of Medical Sciences, Beijing, China. The pool was divided into four quadrants (I, II, III, and IV). A platform (15-cm diameter, 33-cm depth) was submerged 1 cm below the water surface in the center of quadrant IV. Training trials were conducted 5 days prior to surgery. Each rat underwent four training trials per day for 5 days. The rats were initially placed into the different quadrants and given 90 s to locate the hidden platform. If the rat failed to find the platform in the allotted time, it was guided to the platform, allowed to stay for 30 min, and given a score of 90 s. The tests were conducted on postoperative days 7, 14, and 21. The swimming distance (cm), escape latency (s), and average velocity (cm/s) were recorded using the ANY-maze video tracking system (Anymaze, XinRuan Information Technology Co. Ltd., Shanghai, China).

**Sample preparation**

After all rats had completed the behavior tests (postoperative day 21), they were anesthetized. Four rats were then perfused with 0.9% NS and subsequently fixed with 4% paraformalde-
hyde. The hippocampal tissues were removed, and sectioned to 6-μm thickness for histological studies, immunohistochemical analysis, and terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. Four other rats were euthanized, and their hippocampal tissues were removed for western blotting and enzyme-linked immunosorbent assay (ELISA).

**Hematoxylin-eosin staining**
Sections were stained with hematoxylin solution for 1 to 2 min, washed under running tap water, and differentiated in acid ethanol. Samples were counterstained in 0.5% eosin solution.

**Immunohistochemistry**
Astrocyte activation was examined by immunohistochemistry. Sections were probed with rabbit polyclonal anti-glial fibrillary acidic protein (anti-GFAP) primary antibody (1:1000 dilution; Dako, Copenhagen, Denmark). On the second day, the samples were incubated with goat anti-rabbit biotinylated secondary antibody (1:500 dilution; Beijing Zhongshan Golden Bridge Biological Technology Co. Ltd., China), followed by incubation in SABC complex (Vector Laboratories, CA, USA). The antibody binding was visualized with 3, 3’-diaminobenzidine tetrahydrochloride (DAB). Five fields were randomly selected from each immunostained section. Data were analyzed by Qwin V3 software. The degree of astrocyte activation was determined by the following equation: astrocyte activation (%) = (number of activated astrocytes/total number of astrocytes) × 100%.

**Examination of TNF-α, IL-1β and IL-10 production**
The levels of TNF-α, interleukin (IL)-1β and IL-10 in the hippocampus were measured by ELISA. The unilateral hippocampus was dissected, ground with a grinder, and loaded onto an ultrasonic tissue homogenizer. The supernatant was collected, ultracentrifuged for 30 min at 4°C, and stored at −80°C. The protein concentrations of the samples were determined using a BCA assay kit (Beyotime, Shanghai, China). Protein extracts were separated by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and then transferred to polyvinylidene difluoride membranes. The membranes were then blocked and incubated with rabbit monoclonal antibodies against TNF-α, IL-1β, and IL-10 (1:1000 dilution; Santa Cruz, CA, USA), or anti-caspase 3 antibody (1:500 dilution; Santa Cruz, CA, USA). β-actin was used as a loading control. The expression bands of target proteins were analyzed by Scion Image software (version 4.0.3; Scion Co., Santa Cruz, CA, USA). The densitometric values were used to conduct the statistical analysis. The relative protein expression was calculated over β-actin.

**Statistical analysis**
Data were analyzed by SPSS 17.0 software, and are presented as mean±standard deviation. Statistical significance among the groups was determined using one-way analysis of variance. Comparisons between two groups were conducted using the least significant difference t test. All p values <0.05 were considered to be significantly different.

**RESULTS**
HBO prevented learning and memory dysfunction in the HBO+AD group
Before the experiments, no significant differences were ob-
erved in the learning and memory abilities of the rats among
the three groups ($p>0.05$) (Fig. 1A, B and C). Moreover, there
were no statistical differences in the swimming distance, es-
scape latency, or average velocity among the three experimental
groups on postoperative days 7 and 14 ($p>0.05$). However, the
swimming distance and escape latency were significantly ele-
vated in the AD group on day 21, indicating learning and mem-
ory impairment in these rats ($p<0.05$). The learning and mem-
ory dysfunction was partially prevented by HBO pretreatment.
The swimming distance and escape latency were significantly
lower in the AD+HBO than in the AD group on day 21 ($p<0.05$).
Representative results of the track path in rats from different
groups are presented in Fig. 1D. The average velocity did not
change with the different treatments ($p>0.05$).

**HBO prevented neuronal damage and astrocyte
activation in the HBO+AD group**

Next, we investigated the alterations in the hippocampal CA1
region of rats from the three experimental groups. Histological
examination revealed that rats in the NS control group had an
intact hippocampal structure with regularly arranged cells (Fig.
2A). The lightly stained nucleus was relatively large and round
with clear nucleolus formation, and the neurons were rich in
cytoplasm. In contrast, the neurons of rats in the AD group
were loosely distributed and exhibited swelling and vacuola-
tion. The nucleus was darkly stained and condensed, and some
of the neurons showed irregular morphology with small cell
soma. The number of damaged neurons was substantially lower
in the hippocampal CA1 region of rats in the NS than in the
AD group, and the nucleus was morphologically normal in the
NS group. Moreover, the degree of tissue swelling and hippo-
campal abnormalities was significantly lower in the NS group.
As shown in Fig. 2A, the astrocytes in hippocampal CA1 of
the NS group were lightly stained with GFAP and loosely dis-
tributed, and they had small cell bodies and long processes.
The astrocytes in the AD group were darkly stained and exhib-
itied large cell soma and short processes, with the typical char-
acteristics of astrocyte activation. The percentage of activated
astrocytes was much higher in the AD than in the NS group
($p<0.05$) (Fig. 2B). The percentage of astrocyte activation in
the hippocampal CA1 region was significantly lower in the
HBO+AD than in the AD group ($p<0.05$), although no signifi-
cant difference was detected in the percentage of activated as-
astrocytes between the NS and AD+HBO groups ($p>0.05$). Fur-
thermore, the TNF-$\alpha$, IL-1$\beta$, and IL-10 levels in the hippocam-
us were higher in the AD than in the NS group ($p<0.05$), while-
a significantly lower TNF-$\alpha$ elevation was observed in the
HBO+AD than in the AD group ($p<0.05$). No differences were
seen in the IL-1$\beta$ and IL-10 expression level ($p>0.05$) (Fig. 2C).

**HBO prevented loss of dendritic spines in the
HBO+AD group**

As shown in Fig. 3, the AD group showed a predominant loss of
dendritic spine in the hippocampal CA1 region ($p<0.05$), com-
pared with the NS group. In addition, the group given HBO pretreatment showed elevated numbers of AD injury-induced dendritic spines ($p < 0.05$), compared with the AD group.

**HBO prevented apoptosis of neurons in hippocampal CA1 region in the HBO+AD group**

Hippocampal CA1 sections derived from the three experimental groups underwent TUNEL staining. As shown in Fig. 4A, TUNEL-positive cells exhibited condensed chromosomes, and apoptotic bodies were visualized in some of the apoptotic cells. Most of the apoptotic cells showed small cell soma. The rate of cell apoptosis was remarkably higher in the AD than in the NS group ($p < 0.05$) (Fig. 4B). The rate of cell apoptosis in the hippocampal CA1 region was significantly lower in the HBO+AD than in the AD group ($p < 0.05$). The expression of cleaved caspase 3 was increased remarkably in the AD group, and this increase was efficiently reversed by HBO therapy (Fig. 4C and D). These data suggested that the HBO therapy efficiently decreased cell apoptosis in the hippocampal CA1 region.

**HBO reduced p38 MAPK phosphorylation in the hippocampus in the HBO+AD group**

The level of phosphorylated p38 MAPK was determined to investigate the molecular mechanism involved in HBO-associated prevention of cognition decline and neuronal apoptosis in this rat model of AD. The level of phosphorylated p38 MAPK was significantly higher in the hippocampus of rats in the AD than NS group ($p < 0.05$) (Fig. 5). However, the phosphorylated...
p38 MAPK level was significantly lower in the HBO+AD than in the AD group (p<0.05).

DISCUSSION

Although the neuroprotective effects of HBO therapy have been proposed in several rodent disease models, such as spinal cord injury and hypoxia-ischemia, the potential neuroprotective effect of HBO against cognitive decline and hippocampal damage in animal models of AD is not entirely understood. In the present study, we demonstrated for the first time that HBO pretreatment prevents learning and memory decline, hippocampal damage, dendritic spine loss, and astrocyte activation, possibly through inhibition of p38 MAPK activation.

AD is mainly characterized by the deposition of Aβ in the hippocampus and cortex, which lead to neuronal damage and learning and memory decline in affected patients. Evidence indicates that bilateral injection of Aβ1-40 into the CA1 region of the hippocampus induces neurodegeneration, DNA fragmentation, synaptic dysfunction, and impaired cognition in rats. An in vitro study also indicated that Aβ can induce apoptotic and autophagic cell death. In the present study, we found that injection of Aβ1-40 into the CA1 region of the bilateral hippocampus significantly impaired the learning and memory capability of rats 12 days after the initial injection. The cognitive decline was accompanied by an abnormal hippocampal struc-

![Fig. 3. Dendritic spine density in the hippocampal CA1 region. (A) Sections derived from the NS, AD, or AD+HBO group on postoperative day 21 were stained with Golgi-Cox. Magnification, 1000×. (B) The number of dendritic spines per 10 μm was calculated. Ten neurons from each animal were included in the calculation, and two animals from each group were used for analysis. *p<0.05 compared with NS, †p<0.05 compared with AD. NS, normal saline; AD, Alzheimer’s disease; HBO, hyperbaric oxygen.](image)

![Fig. 4. Cell apoptosis in the hippocampal CA1 region. (A) Sections derived from the NS, AD, or AD+HBO group on postoperative day 21 were analyzed by TUNEL assay. Representative images are presented. Magnification, 400×. (B) The percentage of apoptotic cells was calculated. (C) Protein expression of cleaved caspase 3. β-actin was used as a loading control. (D) The relative expression of cleaved caspase 3 was calculated. n=4. *p<0.05 compared with NS, †p<0.05 compared with AD. NS, normal saline; AD, Alzheimer’s disease; HBO, hyperbaric oxygen; TUNEL, terminal deoxynucleotidyl transferase dUTP nick end labeling.](image)
ropathic hyperalgesia in rats by inhibiting astrocyte activation, and reduced the generation of TNF-α release. Notably, the IL-1β and IL-10 levels were not obviously altered following HBO treatment in rats with AD, implying that HBO may have limited effects on IL-1β release. Nevertheless, the underlying mechanism requires further study. HBO therapy was shown to ameliorate the dendritic spine loss in the AD rat model. Since dendritic spine density is correlated with the disease-related memory deficits, we speculate that HBO pretreatment may prevent the characteristic cognitive decline observed in rats with AD, possibly through a mechanism that inhibits dendritic spine loss in the hippocampus.

Activation of p38 MAPK has been found to protect against oxidative stress\(^7\) and apoptosis;\(^2\) however, a growing body of evidence suggests that p38 MAPK mediates pro-apoptotic cascades. The activation of p38 MAPK plays an important role in the pathogenesis of AD. Zhao, et al.\(^5\) described that the rate of p38 MAPK activation was especially high at the site of neurofibrillary tangle and plaque formation. Moreover, p38 MAPK activation in neurons and astrocytes may be induced by the release of cytokines, such as TNF-α and IL-1β.\(^7\) In the present study, we detected a significantly higher rate of p38 MAPK phosphorylation in the hippocampus of rats with AD. HBO pretreatment greatly reduced the rate of p38 MAPK phosphorylation. These findings indicate that HBO pretreatment may reduce neuronal damage and astrocyte activation and subsequently decrease TNF-α production and p38 MAPK phosphorylation, collectively contributing to the improvement of cognitive decline in rats with AD. However, we could not rule out the possibility that the increased p-p38 MAPK level is a consequence, rather than a cause, of AD-like neuronal damage. Blockage of p38 MAPK activation using specific inhibitors may help to understand the underlying mechanism of p38 MAPK-mediated neuronal injury in AD rats. Indeed, an intensive global search is underway for the development of small-molecule p38 MAPK inhibitors that may be useful for AD therapy.\(^25\) We are planning to further investigate the effects of p38 MAPK inhibitors on Aβ deposition-induced learning and memory dysfunction.

In summary, HBO pretreatment greatly improved the learning and memory ability by inhibiting dendritic spine loss and reduced the neuron apoptosis, astrocyte activation, and TNF-α production in the hippocampus of rats with AD. The neuroprotective effects of HBO might be associated with blockade of p38 MAPK activity. Therefore, HBO therapy, a noninvasive, safe, and inexpensive technique, may be useful in elderly patients with AD. Nevertheless, according to the results of the present study, the neuroprotective effects of HBO remain limited, because, although HBO pretreatment partially prevented cognitive decline, neuronal damage, dendritic spine loss and astrocyte activation, these parameters did not return to baseline levels. Therefore, other approaches might be needed to effectively prevent neuronal damage in patients with AD. Although patients are generally tolerant of HBO therapy, the cli-
nical application of HBO is still limited due to its side effects, including neurotoxicity\(^2\) and pulmonary toxicity.\(^{27}\) Therefore, the treatment pressure should be carefully considered when this clinical therapy is applied.

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