Original Paper

3-N-Butylphthalide (NBP) Attenuates the Amyloid-β-Induced Inflammatory Responses in Cultured Astrocytes via the Nuclear Factor-κB Signaling Pathway

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Abstract

Background/Aims: Activation of astrocytes is a common feature of Alzheimer's disease (AD). Proinflammatory molecules produced by activated astrocytes contribute to neuronal damage in AD. Moreover, dl-3-n-butylphthalide (NBP) has been reported to attenuate astroglial activation and exert neuroprotective effects in AD transgenic mice. However, the mechanism by which NBP inhibits activated astrocytes is poorly understood. *Methods:* In this study, the primary astrocytes were obtained from the cerebral cortices of 1-day-old Sprague-Dawley rats. The levels of GFAP, COX-2, NF-κB, and IκBα were examined by Western blotting and the levels of TNF-α and IL-6 were determined by ELISA. *Results:* NBP inhibited the amyloid-β (Aβ)-induced activation of astrocytes and the up-regulation of proinflammatory molecules. Importantly, NBP markedly suppressed Aβ-induced IκBα degradation and nuclear factor-κB (NF-κB) translocation. *Conclusion:* Our results suggest that NBP attenuates Aβ-induced activation of astrocytes and neuroinflammation via inhibition of the NF-κB signaling pathway.

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Introduction

Alzheimer's disease (AD) is a progressive neurodegenerative disorder characterized by a gradual cognitive decline, and there is currently no effective treatment that stops the progression of AD. The prominent neuropathological features in AD are the loss of neurons and the presence of intracellular neurofibrillary tangles and extracellular amyloid plaques.

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Amyloid β-peptide (Aβ) is the major component of amyloid plaques found in the brains of AD patients. Amyloid deposition and the associated neuroinflammation, which contribute to neuronal loss and cognitive decline, have been proposed as pivotal events in the pathogenesis of AD. Neuroinflammation is characterized by astrocytic and microglial activation. Activated astrocytes and microglia are observed in large numbers around amyloid plaques in the brains of AD transgenic animal models and patients. In addition, a variety of proinflammatory molecules, including cyclooxygenase-2 (COX-2), interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and inducible nitric oxide synthase (iNOS), produced by activated glial cells, are elevated in the brains of AD transgenic animal models and patients. Moreover, another proinflammatory molecule, prostaglandin E2 (PGE2), is increased in the cerebrospinal fluid (CSF) of AD patients [1]. These proinflammatory molecules, which can be released by activated astrocytes, contribute to neuronal damage and accelerate the progression of neurodegenerative disorders. Although astrocytes are involved in the neuroinflammatory process, few investigations have been conducted to understand the role of activated astrocytes in the neuroinflammatory process associated with AD.

Nuclear factor-kappa B (NF-κB) is a family of transcription factors that are expressed in a wide variety of cells, including glial cells. NF-κB regulates multiple cellular pathways associated with cell differentiation, cell growth, apoptosis, and stress. NF-κB also regulates the expression of many genes involved in the inflammatory response. The transcriptional activation of NF-κB is tightly regulated by IκBα degradation. In quiescent cells, NF-κB remains inactive in the cytoplasm due to the formation of complexes with the inhibitory protein IκBα. Upon stimulation, IκBα is degraded, which then allows NF-κB to translocate to the nucleus, bind to cognate DNA binding sites, and initiate the transcription of target proinflammatory genes, such as COX-2, TNF-α, and interleukin-1 (IL-1). Increasing evidence suggests that upregulated NF-κB pathway activity is involved in the neurodegenerative process of AD. In the brain of AD patients, p65 immunoreactivity is predominantly found in neurons and astrocytes in the immediate vicinity of amyloid plaques. Enhanced NF-κB activity in resident glial cells might be associated with the increased levels of inflammatory mediators in the brain and drive progressive neurotoxicity. Therefore, modulating glial activation and associated neuroinflammation may be beneficial in the prevention of AD.

Dl-3-n-butylphthalide (NBP), a drug commonly used to treat acute ischemic stroke in China, has been found to reduce Aβ-induced neurotoxicity in rat hippocampal neurons and human neuroblastoma SH-SY5Y cells [2]. A recent study found that NBP could attenuate astroglial activation and improve cognitive function in AD transgenic mice [3]. However, the mechanism by which NBP inhibits activated astrocytes has not been fully elucidated.

In our study, we determined that Aβ induced the up-regulation of proinflammatory molecules (including COX-2, PGE2, TNF-α, and IL-6) in cultured astrocytes, which can be markedly reversed by the addition of NBP. Our results demonstrated that NBP could suppress Aβ-induced proinflammatory molecules by inhibiting IκBα degradation and NF-κB activation. Taken together, our study suggested that NBP exerts anti-inflammatory effects, at least partially, by modulating the NF-κB signaling pathway. Therefore, NBP might have considerable potential for the treatment of AD.

Materials and Methods

Antibodies and reagents

NBP was kindly provided by the Shijiazhuang Pharma Group NBP Pharmaceutical Co. Ltd. NBP was dissolved in dimethylsulfoxide (DMSO). 3-(4,5-Dimethylthiazol-2-yl)-2, Dulbecco's Modified Eagle Medium (DMEM), 5-diphenyltetrazoliumbromide (MTT), and fetal bovine serum were obtained from Invitrogen (Carlsbad, CA, USA). The antibody against glial fibrillary acidic protein (GFAP) and $A\beta_{1-42}$ peptide were from Sigma Aldrich (St. Louis, MO, USA). $A\beta_{1-42}$ peptide was dissolved in double-distilled water and incubated for 7 days at 37 °C to form aggregated amyloid. Anti-Lamin B1 antibody was obtained from Abcam (Cambridge, MA, USA). The antibody against IκBα was obtained from Cell Signaling Technology (Beverly, MA, USA).

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All other antibodies were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). The TNF-α ELISA assay kit was from R&D Systems (Minneapolis, MN, USA). The IL-6 ELISA assay kit was purchased from BD Biosciences Pharmingen (San Diego, CA, USA). The PGE2 enzyme immunoassay kit was obtained from Cayman Chemical (Ann Arbor, MI, USA). The Nuclear and Cytoplasmic Protein Extraction Kit was from the Beyotime Institute of Biotechnology (Nantong, Jiangsu, China). All other chemicals were purchased from Sigma unless otherwise indicated.

Astrocyte cultures

Primary astrocytes were obtained from the cerebral cortices of 1-day-old Sprague-Dawley rats as previously described [4]. The cells were plated in culture flasks and maintained at 37 °C in a humidified atmosphere of 5% CO_2 and 95% air. After approximately 12 days, the confluent cultures were shaken (200 rpm, 4 h) to separate the astrocytes from the remaining microglia and oligodendrocytes. The purity (95%) of the astrocyte cultures was confirmed using an anti-GFAP antibody.

Cell viability assays

The viability of the astrocytes was evaluated by MTT assay as previously described [5]. In brief, the cells were treated with NBP for 24 h. MTT (0.5 mg/ml) was added to the medium and incubated for an additional 4 h. At the end of the incubation period, the medium with MTT was removed, and 100 µl DMSO was subsequently added to each well. The absorbance at 570 nm was measured using a microplate reader. The cell viability was expressed as a percentage of the control culture (100%).

Western blot analyses

To determine the levels of GFAP, COX-2, and IκBα, total cell lysates were prepared as previously described [4]. Nuclear and cytosol fractions were prepared to assess the expression of NF-κB (p65). Samples containing 25 µg of the protein extracts were subjected to SDS–PAGE and transferred to PVDF membranes. The membranes were blocked for 1 hour with 5% fat-free milk in TBST buffer (150 mM NaCl, 50 mM Tris-HCl pH 7.4, 0.05% Tween 20) and then incubated with the primary antibodies at 4 °C overnight. The membranes were washed and subsequently exposed to the appropriate horseradish peroxidase-conjugated secondary antibodies for 1 h at room temperature. After three washes in TBST, the bands were detected with enhanced chemiluminescence.

TNF-α assay, IL-6 assay, and PGE2 assay

The levels of TNF-α and IL-6 were determined by an ELISA detection kit according to the manufacturer's instructions. The level of prostaglandin E2 was measured by a PGE2 enzyme immunoassay kit (Cayman Chemicals, Ann Arbor, MI) following the manufacturer's instructions.

Statistical analysis

All data are expressed as the means ± standard error of the mean (SEM). The statistical significance of the differences was assessed using one-way ANOVA, followed by Bonferroni's t test. A value of $p < 0.05$ was considered statistically significant.

Results

Effect of NBP on cellular viability of astrocytes

The primary astrocytes were obtained from the cerebral cortices of 1-day-old Sprague-Dawley rats. The cultured primary astrocytes were treated with NBP (0.1-100 µM) for 24 h, and the cellular viability was measured by the MTT assay. Compared with the control group, 0.1-10 µM NBP did not affect the viability of the astrocytes, whereas 100 µM of NBP significantly ($p < 0.05$) reduced the viability of the astrocytes (Fig. 1). Therefore, nontoxic concentrations of NBP (0.1-10 µM) were used in the subsequent experiments.

NBP inhibited the levels of COX-2 and GFAP in the Aβ-treated astrocytes

We further investigated the levels of GFAP and COX-2 in the $Aβ_{1-42}$-treated astrocytes. The results showed that $Aβ_{1-42}$ treatment increased the levels of GFAP and COX-2 in the

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Fig. 1. Effect of NBP on the cellular viability of astrocytes. Cells were untreated or incubated with NBP (0.1-100 μM) for 24 h, and the cellular viability was detected by MTT. Experiments were performed in triplicate and repeated in three separate cell preparations. The data are presented as the means ± SEM. * p<0.05 compared with the control.
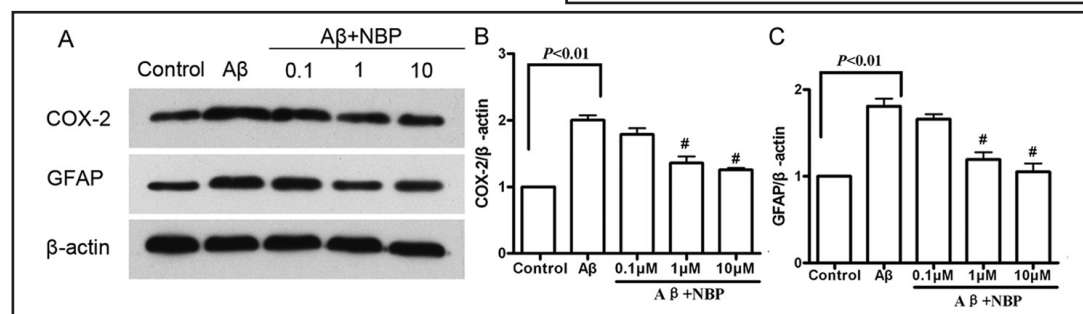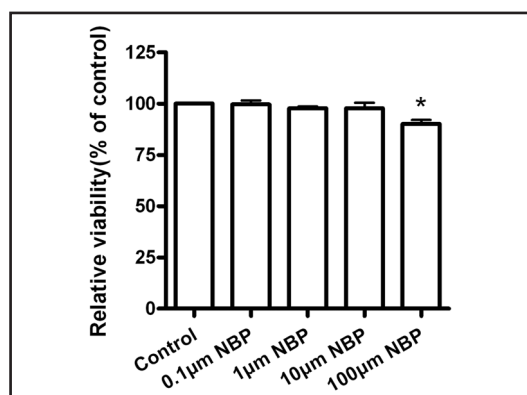
Fig. 2. Effect of NBP on the levels of GFAP and COX-2 in Aβ-treated astrocytes. Cells were treated with 10 μM Aβ$_{1-42}$ for 24 h, or pre-incubated with NBP (0.1-10 μM) for 30 min prior to treatment with 10 μM Aβ$_{1-42}$ for 24 h. Then the COX-2 and GFAP protein expressions were measured by western blotting. (B and C) Protein bands quantified by densitometry are expressed as the means ± SEM. The experiments were repeated in three separate cell cultures. #p<0.01 versus Aβ-treated group.

astrocytes. Then, we examined the effect of NBP on the levels of GFAP and COX-2 in the Aβ$_{1-42}$-treated astrocytes. After the cells were treated with 10 μM Aβ$_{1-42}$ for 24 hours, or pre-incubated with NBP (0.1-10 μM) for 30 min prior to treatment with 10 μM Aβ$_{1-42}$ for 24 hours, western blotting was performed to test the level of GFAP and COX-2 expression. NBP (1-10 μM) obviously inhibited Aβ$_{1-42}$-induced up-regulation of GFAP and COX-2 (Fig. 2). Nevertheless, low-dose NBP (0.1 μM) failed to attenuate Aβ$_{1-42}$-induced up-regulation of GFAP and COX-2.

NBP attenuated NF-κB (p65) nuclear translocation and IκBα degradation in Aβ-treated astrocytes

Our previous study found that Aβ$_{25-35}$ induces the NF-κB (p65) nuclear translocation in astrocytes, thereby increasing the production of proinflammatory molecules such as COX-2 [4]. In this study, we investigated the effect of NBP on NF-κB (p65) nuclear translocation in Aβ$_{1-42}$-treated astrocytes. The cells were treated with 10 μM Aβ$_{1-42}$ for 24 hours or pre-incubated with NBP (0.1-10 μM) for 30 min prior to treatment with 10 μM Aβ$_{1-42}$ for 24 hours, and NF-κB (p65) protein expression was detected by western blotting. As shown in Fig. 3A and B, Aβ$_{1-42}$ treatment significantly increased NF-κB (p65) nuclear translocation, which could be suppressed by NBP pretreatment.

It was reported that the activity of NF-κB (p65) is tightly regulated by the cytoplasmic inhibitory protein IκBα. Therefore, we further assessed the protein expression of IκBα. As shown in Fig. 3C, Aβ$_{1-42}$ dramatically induced the degradation of IκBα, which can be attenuated by pretreatment with NBP. This result was consistent with the result of NF-κB (p65) protein expression. NBP at concentrations ranging from 1-10 μM exhibited an inhibitory effect in a dose-dependent manner, whereas 0.1 μM NBP failed to attenuate Aβ$_{1-42}$-induced NF-κB (p65) nuclear translocation and IκBα degradation.

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Fig. 3. Effect of NBP on NF-κB (p65) nuclear translocation and IκBα expression in Aβ-treated astrocytes. (A) The cells were treated as described in Fig. 2A. The protein expression of NF-κB (p65) in nuclear extracts was measured by western blotting. Lamin B1 was used as a loading control for nuclear protein. Protein bands quantified by densitometry are expressed as the means ± SEM. The experiments were repeated in three separate cell cultures. #p<0.01 versus Aβ-treated group. (B) The cells were treated as described in Fig. 2A. The protein expression of NF-κB (p65) in cytosolic extracts was measured by western blotting. β-actin was used as a loading control. Protein bands quantified by densitometry were expressed as the means ± SEM. The experiments were repeated in three separate cell cultures. #p<0.01 versus Aβ-treated group. (C) The cells were treated as described in Fig. 2A. The protein expression of IκBα was measured by western blotting. GAPDH was used as an internal control. The protein bands were quantified by densitometry and are expressed as the means ± SEM. The experiments were repeated in three separate cell cultures. *p<0.05 versus Aβ-treated group; #p<0.01 versus Aβ-treated group.
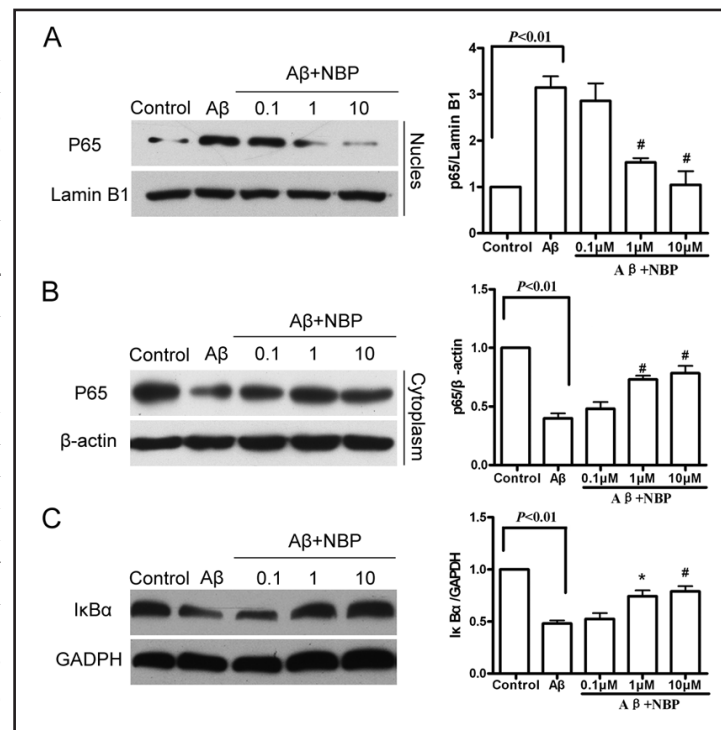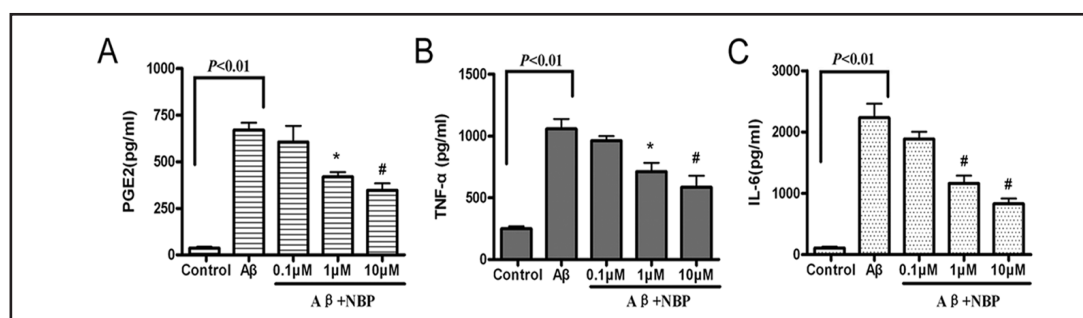
NBP suppressed the levels of PGE2, TNF-α, and IL-6 in Aβ-treated astrocytes

Increasing evidence suggests that PGE2 and TNF-α contribute to ongoing neuronal degeneration in AD. TNF-α can induce neuronal apoptosis in specific contexts [6] and play a role in the pathogenesis of AD [7]. Moreover, IL-6 is enhanced in AD brain and might contribute to inflammatory responses in AD. Therefore, we measured the effects of the $A\beta_{1-42}$ and NBP on PGE2, TNF-α, and IL-6 levels in astrocytes. As shown in Fig. 4A-C, $A\beta_{1-42}$ markedly increased the levels of PGE2, TNF-α, and IL-6 in astrocytes, whereas NBP (1-10 μM) significantly reduced $A\beta_{1-42}$-induced up-regulation of PGE2, TNF-α, and IL-6. Consistent with the results of NF-κB (p65) nuclear translocation and IκBα degradation, NBP (1-10 μM) inhibited $A\beta_{1-42}$-induced up-regulation of proinflammatory molecules, including COX-2, PGE2, TNF-α, and IL-6 in a dose-dependent manner, whereas 0.1 μM NBP failed to alter $A\beta_{1-42}$-induced up-regulation of proinflammatory molecules in astrocytes.

Discussion

Astrocytes are the most numerous cells in the brain and play an important role in neuronal function. They control the extracellular K+ homeostasis and extracellular levels of glutamate, regulate the blood–brain barrier, participate in synaptic transmission, and shape the microarchitecture of the brain [8-10]. Recently, increasing evidence suggests that activated astrocytes are involved in the pathogenesis of AD [11-13]. Abundant reactive astrocytes are characteristically found near amyloid plaques in AD brains [14], and the typical astrocyte marker GFAP is elevated in AβPP transgenic mice and AD patients. Activated astrocytes can produce proinflammatory molecules and play a role in plaque formation [14].

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Fig. 4. Effect of NBP on the levels of PGE2, TNF-α, and IL-6 in Aβ-treated astrocytes. (A) The cells were treated as described in Fig. 2A. The production of PGE2 was determined by ELISA. The experiments were performed in triplicate and repeated in three separate cell preparations. The data are presented as the means ± SEM. *p<0.05 versus Aβ-treated group; #p<0.01 versus Aβ-treated group. (B) The cells were treated as described in Fig. 2A. The production of TNF-α was detected by ELISA. The experiments were performed in triplicate and repeated in three separate cell preparations. The data are presented as the means ± SEM. *p<0.05 versus Aβ-treated group; #p<0.01 versus Aβ-treated group. (C) The cells were treated as described in Fig. 2. The production of IL-6 was detected by ELISA. The experiments were performed in triplicate and repeated in three separate cell preparations. The data are presented as the means ± SEM. #p<0.01 versus the Aβ-treated group.

Accumulating evidence indicates that a variety of proinflammatory cytokines and other immune neurotoxins are detected in both the cerebrospinal fluid (CSF) and the affected brain regions of AD patients [15-18]. TNF-α, an important factor involved in the regulation of neuronal apoptosis, was found to be increased in the brains of APPswe/PS1dE9 mice. In addition, agents reducing PGE2 synthesis were shown to be neuroprotective in an animal model of AD [19], whereas administration of a TNF-α antagonist can improve the cognitive function of AD patients [20]. These studies suggest that the inflammatory response plays an important role in the pathogenesis of AD.

NF-κB is considered a primary regulator of inflammatory processes. Following cellular stimulation, NF-κB releases from IκBα, enters the nucleus, and promotes the transcription of its target genes. Activation of NF-κB leads to the expression of a large variety of proinflammatory molecules that can damage and kill neurons. Previous studies have revealed that increased NF-κB activity can induce neuronal death and is involved in the neurodegenerative process of AD. In the AD brain, NF-κB immunoreactivity is higher in astrocytes surrounding amyloid plaques. In this study, we found that the expression of GFAP was markedly elevated in $Aβ_{1-42}$-treated astrocytes. In line with the enhanced level of GFAP, proinflammatory molecules (including COX-2, PGE2, TNF-α and IL-6) were notably increased in astrocytes treated with $Aβ_{1-42}$. These observations suggested that $Aβ_{1-42}$ treatments induced the activation of astrocytes as well as the up-regulation of proinflammatory molecules. Moreover, $Aβ_{1-42}$ stimulation increased both IκBα degradation and NF-κB nuclear translocation, indicating that the NF-κB signaling pathway participates in the $Aβ_{1-42}$-induced inflammatory response in astrocytes. Taken together, these findings suggested that the $Aβ_{1-42}$ treatment induced the degradation of IκBα and NF-κB nuclear translocation, leading to the up-regulation of PGE2, TNF-α, and IL-6 in primary astrocytes. Therefore, blocking NF-κB activation might be an effective strategy in the treatment of AD.

NBP is a multi-target drug for the treatment of acute ischemic stroke in China. NBP exhibits protective effects against focal cerebral ischemia in animal models through the prevention of mitochondrial damage, the inhibition of neuronal apoptosis, the improvement of cerebral blood flow, and the reduction of infarct volume [21-23]. Our previous studies demonstrated that NBP could significantly inhibit caspase-3-mediated apoptosis after cerebral ischemia in diabetic rats [24]; and NBP administration could attenuate stroke-induced neuron loss and activation of astrocytes in diabetic rats [25]. However, several studies showed that NBP

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has protective effects against Aβ-induced neuronal injury. Peng et al. reported that NBP reduces Aβ-induced neurotoxicity in rat hippocampal neurons and human neuroblastoma SH-SY5Y cells [2]. It was also demonstrated that NBP could improve cognitive function and inhibit glial activation in AD transgenic mice [3]. However, the mechanism underlying the anti-inflammatory effect of NBP is still poorly understood. In the present study, we observed the mechanism by which NBP exerts anti-inflammatory effects on $Aβ_{1-42}$-treated astrocytes. We confirmed that NBP pretreatment not only inhibited $Aβ_{1-42}$-induced activation of astrocytes, but it also suppressed the up-regulation of COX-2, PGE2, TNF-α, and IL-6 triggered by $Aβ_{1-42}$. Importantly, $Aβ_{1-42}$-induced IκBα degradation and NF-κB nuclear translocation were markedly inhibited by NBP pretreatment. These results supported the hypothesis that NBP acts as a potential NF-κB inhibitor. Although we can conclude that the NF-κB signaling pathway plays a role in the inflammatory response induced by Aβ, we cannot rule out the involvement of other signaling pathways that were not investigated in this study. For example, calcineurin expression is upregulated in activated astrocytes in AD model brains, and calcineurin/NFAT (Nuclear Factor of Activated T-cells) activity is elevated in postmortem human tissue at very early stages of AD [11]. It has been shown that calcineurin regulates cytokine production through the activation of NFAT, and the calcineurin/NFAT pathway is highly sensitive to Aβ and obviously promotes cytokine production in astrocytes [11]. Furman JL et al. recently reported that selective inhibition of calcineurin/NFAT pathway in astrocytes decreased glial activation and other AD biomarkers in AD model mice [13]. In the present study, we did not achieve a total inhibition of Aβ-induced NF-κB nuclear translocation and IκBα degradation in astrocytes treated with NBP. Therefore, we cannot exclude the possibility that other pathways, such as calcineurin/NFAT, might participate in the anti-inflammatory effects of NBP. Taken together, the present study's results indicate that NBP exerts anti-inflammatory effects, at least partially, through the inhibition of NF-κB signaling pathways, thereby resulting in the reduction of proinflammatory molecules in $Aβ_{1-42}$-treated astrocytes. These findings suggest that NBP has considerable potential for the treatment of AD.

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