Research Article
Effects of Brain-Derived Neurotrophic Factor on Local Inflammation in Experimental Stroke of Rat

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1. Introduction

Stroke is a major cause of death and long-term disability worldwide [1, 2]. Brain-derived neurotrophic factor (BDNF) can decrease infarct volume and improve neurological outcome either by exogenously supplied or overexpression in vivo using genetic methods in experimental stroke. Inhibition of BDNF exaggerates damage of ischemia. BDNF exerts neuron protection against ischemic injury through binding to two membrane receptors, p75 neurotrophin receptor and tyrosine kinase receptor B (trkB) [3]. 7,8-dihydroxyflavone as a bioactive high-affinity TrkB agonist also protects neurons from apoptosis and decreases infarct volumes in animal model of stroke [4].

Inflammation plays an essential role in the pathogenesis of ischemic stroke [5, 6]. Rapid activation of resident inflammatory cells (mostly microglia), productions of inflammatory cytokines such as interleukin10 (IL-10) and tumor necrosis factor α (TNF-α) and translocation of intercellular transcription factors such as nuclear factor-kappa B (NF-κB) are characters of local inflammatory responses to ischemia in brain [7–11]. Different responses may have different functions in the pathogenesis of stroke. Activated microglia could excrete neurotrophic effects such as BDNF to alleviate ischemic injury and exhibit phagocytic activity disposing of degenerating elements [7, 11]. There are several cytokines involved in inflammatory process. TNF-α, as an important proinflammatory cytokine, appears to exacerbate cerebral injury of ischemia [8] while IL-10, an anti-inflammatory cytokine, ameliorates ischemic insult of brain [9]. Activation of NF-κB, an important transcription factor, could mediate translation of many downstream genes and promote survival of neurons [10].

BDNF promotes cell proliferation, increases phagocytic activity and inhibits apoptosis of microglia in brain [12]. BDNF downregulates the expression of TNF-α and upregulates the expression of IL10 in the model of multiple sclerosis [13]. NF-κB activated by BDNF protects cells from damages, such as the serum starvation and glutamate toxicity [14]. However, whether BDNF modulates inflammatory processes in ischemic stroke is unclear. In present study, we evaluated...
of ischemic stroke [6]. Exogenous administration of TNF-α exacerbates ischemic brain injury while inhibition of TNF-α could reduce brain damage [8, 28]. BDNF could provide protection of brain in ischemic stroke via decreasing local TNF-α.

BDNF not only decreased local proinflammatory cytokine, it also increased local anti-inflammatory cytokine. IL10 is an important anti-inflammatory cytokine. Our data showed BDNF increased the level of IL10 and upregulated the mRNA expression of IL10 at 24 h of reperfusion. Once activity of endogenous BDNF was blocked by BDNF antibody, local IL-10 and its mRNA in brain were increased. These results were consistent with other studies [13]. Previous publications showed that exogenous pre/postischemic administration of IL10 can provide neuroprotection following MCAO [9, 29]. Over-expression of IL10 in vivo markedly protected cortical tissue against cerebral ischemia using the IL10 transgene mice [30]. Our data suggested that BDNF might protect brain from ischemia through upregulating local IL10 in brain.

On the transcription level of local inflammation in brain in ischemic stroke of rats, we found that exogenous BDNF increased the DNA-binding activity of NF-κB. We also provided evidence that the DNA-binding activity of NF-κB was inhibited when the effect of BDNF was suppressed. These results indicated that BDNF could modulate NF-κB activity. The way BDNF activates NF-κB in different cells is through the TrkB-PI3-kinase-Akt pathway [31]. Inhibition of TrkB, the receptor of BDNF in the cell, decreases the activation of NF-κB [32]. The activation of NF-κB induced by BDNF protects cells from a variety of damages, including the serum starvation, glutamate toxicity and ischemia [14]. Once the activity of NF-κB was inhibited by different inhibitors, the protections of BDNF against different damages were lessened [31]. Our data suggested that NF-κB played an important role in neuron protection of BDNF.

In our study, effect of BDNF on local inflammation in brain showed no significant difference between antibody group and control group 24 h after reperfusion. This may because that BDNF antibody only blocked the activity of BDNF and may not suppressed the expression of local BDNF in brain after stroke. Our data showed that BDNF antibody did not change BDNF level (Figure 1). 24 h after reperfusion (25 h after BDNF antibody was given), the expression of new BDNF may replace the antibody-conjuncted BDNF; so the effect of BDNF antibody might be removed.

5. Conclusions

In summary, our data suggested that BDNF may alleviate cellular injury of ischemic insult, reduce the neurologic deficits and modulate local inflammation on cellular level, cytokine level, and transcription factor level in ischemic stroke.

Conflict of Interests

The authors have no conflict of interests to disclosure.

Authors’ Contributions

Y. Jiang, N. Wei, and X. Liu participated in concept and design of the study, acquisition of raw data, analysis and interpretation of data, drafting manuscript, critical revision of the manuscript for scientific validity, statistical analysis. J. Zhu, T. Lu, Z. Chen and G. Xu participated in study concept and design, acquisition of raw data and critical revisions of the paper. Y. Jiang and N. Wei contributed equally to this work.

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