Inflammation in the pathogenesis and progression of neurological diseases

Inflamação na patogênese e progressão de doenças neurológicas

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ABSTRACT

Neuroinflammation has been considered a key feature of several neurological disorders such as Alzheimer’s and Parkinson’s diseases and it is an important promoter of brain damage in stroke. It is not completely clear whether inflammatory responses occur as a consequence of the brain injury or it contributes to the pathogenesis of neurological dysfunction. Several mediators participate in the inflammatory response in the central nervous system and some of them, such as the transcription factor NFkB, have a dual role in neurological diseases: enhancement of inflammation and upregulation of cytoprotective molecules. This review discusses some of the recent findings on the role of cytoprotective molecules (A20, Bcl-2 and HO-1) upregulated by NFkB in the context of neuroinflammation and neurodegeneration.

RESUMO

Tem sido observado que a neuroinflamação desempenha um papel importante em diversas patologias neurológicas, tais como doenças de Alzheimer e de Parkinson, além de ser um importante causador de danos neurais relacionados aos acidentes vasculares encefálicos. Entretanto, não está claro se as respostas inflamatórias ocorrem como uma consequência do dano neural ou se elas contribuem para a patogênese da disfunção neurológica. Diversos mediadores participam da resposta inflamatória no sistema nervoso central e alguns dos mesmos, como o fator de transcrição NFκB, desempenham um papel ambíguo nas doenças neurológicas: intensificação da inflamação, bem como aumento da expressão de moléculas citoprotetoras. Esta revisão discute alguns dos resultados recentes sobre o papel de moléculas citoprotetoras (A20, Bcl-2 and HO-1) reguladas positivamente pelo NFκB no contexto dos processos neuroinflamatório e neurodegeragativo.

PALAVRAS-CHAVE

Neurodegeneração - Fator nuclear kappa B - Inflamação.

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INTRODUCTION

Inflammation is a biological response to several noxious stimuli. The intensity of the inflammatory response is rather variable, and can elicit protection by activation of the immune system. However, intensified inflammatory stimulation might promote exacerbation of harmful tissue conditions resulting in activation of signaling pathways and eventually culminating in cell death.

Several mediators are involved in the inflammatory signaling. Interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor-a (TNF-a) are the most important pro-inflammatory cytokines upregulated and secreted during inflammation. These molecules are released by resident and immune cells acting mainly as autocrine and paracrine mediators to coordinate the inflammatory response (Pober e Cotran, 1990). Chemokines are chemotactic cytokines that also play a key role as inflammatory mediators. They are responsible for stimulation of leucocyte migration, which is a hallmark of inflammation (Feng, 2000). In concert with chemokines, a class of proteins named adhesion molecules has a pivotal role in coordinating leukocyte-endothelial cell interactions in order to promote leukocyte migration to the injured tissue in a targeted fashion (Walzog e Gaehhtgens, 2000). Therefore, the inflammatory response depends on an orchestrated interaction between different classes of mediators.

Nuclear transcription factor kappa B (NFkB) is the main intracellular molecule activated by cytokine stimulation. In resting state, latent NFkB is located in the cytoplasm bound to its inhibitory protein IKB-a. In response to pro-inflammatory stimulation (e.g., TNF, IL-1 and lipopolysaccharide – LPS), activated IKK phosphorylates IKB-a leading to its ubiquitination and proteosomal degradation, thus allowing subsequent translocation of active NFkB to the nucleus, where it modulates transcription of several genes. As a result, there is an enhancement in the cellular inflammatory response, with upregulation of adhesion molecules, cytokines, chemokines and many others inflammatory modulators (Schreck, Albermann et al., 1992; Baldwin, 1996). However, there are NFkB-dependent genes that may provide cytoprotection, such as A20, heme-oxygenase 1 (HO-1) and Bcl-2. These molecules are stimulated in response to inflammatory stimuli, but instead of enhancing inflammation, they are able to shut down pro-inflammatory signaling promoting a negative feedback loop to NFkB activation (Ferran, 2006).

In the central nervous system (CNS), modulation of inflammatory responses is attributed primarily to microglial cells, which are the macrophages of the brain. Microglial activation is a key feature after several types of CNS injury aiming to provide host defense and neuronal survival. This phenomenon involves morphological and biochemical changes in microglial cells, such as modification from their quiescent ramified aspect into round and ameboid shape, and increased expression of surface markers (Block, Zecca et al., 2007). However, an exacerbated microglial response might lead to deleterious effects for neural function due to an augmented production of neurotoxic factors. Pro-inflammatory cytokines, such as TNF-a, IL-6 and IL1-b are commonly increased in response to microglia activation, which is a hallmark of the pathophysiology of several neurodegenerative diseases (Sawada, Kondo et al., 1989). Given the importance of balanced microglial response, many studies have been focused on the modulation of this event.

This review aims to describe what is known up to now on the role of some cytoprotective molecules upregulated during inflammatory stimulation in the CNS and the role of inflammation in the pathogenesis of neurological diseases.

Cytoprotective proteins stimulated by inflammation

A20 is an anti-inflammatory NF-kB dependent zinc-finger protein expressed in several cell types. The crucial role of this protein in the inflammatory process can be observed by the fact that A20 knockout mice die within 4-5 weeks of age due to cachexia and generalized chronic inflammation. Basically, A20 is upregulated in response to several NFkB activators such as TNF-a and LPS, and exerts a strong anti-inflammatory function through inhibition of NFkB activation by preventing IKK complex activation and consequently IKB-a degradation (Heyninck et al., 1999; Daniel et al., 2004; Wertz et al., 2004; Kunter et al., 2005; Shembade et al., 2010). The anti-inflammatory effect of A20 has been demonstrated in allergic airway inflammation
Inflammation in the pathogenesis of Alzheimer’s disease

Alzheimer’s disease (AD) is the main cause of dementia in the senescence. It is associated with increased amounts of amyloid-β protein throughout the brain, which may be found as amyloid-β plaques. Besides amyloid-β plaques formation, (Sawada et al., 1989; Hung et al., 2008) another hallmark of Alzheimer’s disease is the presence of neurofibrillary tangles in the brain, which may be found as amyloid-β plaques. Despite of being considered a protective molecule, it has been discussed whether increased amounts of HO-1 in the brain may raise iron deposits leading to higher oxidative stress and subsequent cellular damage (Schipper, 2010). Therefore, the exact role of HO-1 in the CNS is not completely unraveled.

Inflammation and neurodegenerative diseases

Alzheimer’s disease

Alzheimer’s disease (AD) is the main cause of dementia in the senescence. It is associated with increased amounts of amyloid-β protein throughout the brain, which may be found as amyloid-β plaques. The role of Bcl-2 family members in cell death/survival is mainly attributed by their ability to regulate mitochondrial permeabilization, cytochrome C release and caspases activation. This family of proteins comprises both anti and pro-apoptotic molecules. Thus, cellular fate is highly dependent on the levels of these proteins. It is well known that Bcl-2 is a potent anti-apoptotic protein in a number of cell types. Additionally, in the last years other functions of Bcl-2 have emerged, such as regulation of cell cycle (O’reilly et al., 1997), involvement in cellular differentiation (Hilton et al., 1997) and modulation of the activity of transcription factors interfering in gene expression (Feng et al., 2004). In endothelial cells, Bcl-2 and Bcl-XL, another anti-apoptotic Bcl-2 family member, have shown to inhibit NFkB nuclear translocation and consequently downregulate genes related to inflammatory response (Badrichani et al., 1999). In addition, it was demonstrated that overexpression of Bcl-2 in a mouse model of heart disease attenuated myocardial inflammation improving cardiac function (Niu et al., 2006). In the nervous system, Bcl-2 also presents important functions by modulating synaptic plasticity and it was reported that a polymorphism in the Bcl-2 gene is related to lower gray matter volume, which might predispose to mood disorders. Thus, Bcl-2 function in the central nervous system goes beyond to modulation of inflammation and apoptosis (Salvadore et al., 2009).

HO-1 is a cytoprotective heat shock protein induced by a variety of stimuli such as hypoxia, heat stress, radiation, oxidative stress. However, its activation also occurs physiologically to metabolize intracellular heme complex into carbon monoxide, ferrous iron and biliverdin, which is subsequently converted to bilirubin. In addition, it has been described the role of HO-1 as anti-inflammatory and as an immune system modulator. Heme compound is important, for example, to provide binding sites for oxygen in the hemoglobin and myoglobin molecules. However, when heme is removed from proteins it becomes a potent prooxidant agent (Kumar e Bandyopadhyay, 2005). Thus, HO-1 may provide cytoprotection preventing the harmful effect of increased levels of free-heme by metabolizing pro-oxidant and pro-inflammatory heme to produce radical scavengers with anti-inflammatory properties instead (Paine et al., 2010). Bilirubin has been described as an antioxidant and anti-inflammatory compound preventing endothelial activation and decreasing leucocyte migration to the inflammatory sites (Kawamura et al., 2005; Keshavan et al., 2005) and carbon monoxide also presents anti-inflammatory functions by acting as a signaling molecule that downregulates inflammatory cytokines production (Wang et al., 2009). In an unstressed brain, HO-1 is only expressed in small cell populations. However, after traumatic brain injury (Fukuda et al., 1995; Fukuda et al., 1996) (Wang et al., 2009), Parkinson’s and Alzheimer’s diseases (Sawada et al., 1989; Hung et al., 2008) there is upregulation of HO-1 throughout the brain. Despite of being considered a protective molecule, it has been discussed whether increased amounts of HO-1 in the brain may raise iron deposits leading to higher oxidative stress and subsequent cellular damage (Schipper, 2010). Therefore, the exact role of HO-1 in the CNS is not completely unraveled.
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neuronal cells. This pathomorphological modification occurs by phosphorylation of microtubules-associated protein tau (Gouras et al., 2010).

The involvement of inflammation in AD is well-established. However, it is not clear if inflammation is a consequence of the disease or it may contribute to the pathogenesis of AD. It was demonstrated that there is a correlation between increased production of cytokines – TNF-a and IL-1 – by peripheral blood monocytes and higher risk to develop clinical AD (Tan et al., 2007). A common feature in brain areas damaged by AD is the presence of activated microglia close to amyloid-b deposits. As a consequence, there is high release of pro-inflammatory mediators by microglial cells and upregulation of major histocompatibility complex and complement receptors, contributing to further inflammation and neural cells death (Querfurth e Laferla, 2010). Although there is no clear evidence for blood brain barrier disruption or leucocyte migration to the brain in AD, chemokines are upregulated in the serum and brain of AD patients (Lee et al., 2009). It was found that microglia obtained from autopsies of AD patients compared to non-demented individuals has increased expression of the chemokines interleukin-8 (IL-8), monocyte chemoattractant protein 1 (MCP-1) and macrophage inflammatory peptide-1alpha (MIP-1α) after amyloid-b treatment (Lue et al., 2001). Thus, chemokines may regulate microglial and astrocytes recruitment to the neuroinflammation areas.

IL-1β is one of main cytokines increased in the brain tissue in AD. It exerts an important role in neuroinflammation by enhancing IL-6 and iNOS production (Heneka et al., 2010). IL-1β may also contribute to dysfunction of cholinergic neurotransmission, which is another feature of AD, by increasing acetylcholinesterase activity and downregulating muscarinic acetylcholine receptors (mAChR) (Schliebs et al., 2006).

In addition, NFkB signaling pathway is well recognized as the main inflammatory cascade in AD. It has been shown that amyloid-b activates NFkB through the tumor necrosis factor receptor 1 (TNFR1) signaling cascade resulting in neuronal cell death (Li et al., 2004). On the other hand, NFkB activation also leads to increased expression of protective factors. Thus, the outcome of NFkB activation depends on different influences. Particularly in the CNS, the age seems to be a critical issue. Patel and Brewer (Patel e Brewer, 2008) demonstrated that age-related changes to the TNFR1 and TNFR2 signaling result in higher NFkB translocation to the nucleus providing neuroprotection to middle-age neurons, but not in old neurons, because it was found lower Bcl-2 expression in response to NFkB activation in aged neuronal cells. Furthermore, overexpression of Bcl-2 prevented amyloid-b plaques and neurofibrillary tangles formation and also improved memory retention in an AD mouse model (Rohn et al., 2008). The mechanism by which Bcl-2 seems to interfere in the pathophysiology of AD is through inhibition of caspases pathways and consequently diminished cleavage of amyloid precursor protein (APP) and tau protein (Gamblin et al., 2003). Hence, the importance of Bcl-2 in the pathogenesis of AD is clear, but the underlying molecular mechanism is still unknown. Recently, Wang et al. (Wang et al., 2009) have shown that the microRNA mir-34a is overexpressed in an animal model of AD and there is a correlation between increased mir-34a and reduced Bcl-2 levels. MicroRNAs are short regulatory RNAs that modulate protein expression by inhibiting mRNA translation or promoting mRNA degradation. So, this posttranscriptional regulation of Bcl-2 by microRNA may contribute to the pathogenesis of AD.

On the other hand, HO-1, which is generally accepted as a cytoprotective molecule, has been also described as a potential pathogenic player in AD (Schipper, 2010). Excessive heme degradation may generate toxic levels of iron, compromising the redox state of the cellular environment. In astrocytes, HO-1 is stimulated in response to IL-1β, TNF-α and amyloid-b. As a consequence there is oxidative damage mainly by pathological iron deposition. HO-1 inhibitors have been tested as potential therapeutic drugs against AD (Schipper et al., 2009). Hence, the importance of Bcl-2 in the pathogenesis of AD is not completely clear and the underlying molecular mechanism is still unknown. Thus, the pathogenesis of AD may be related to HO-1 increased expression. HO-1 inhibitors have been tested as potential therapeutic drugs against AD (Schipper et al., 2009).

Parkinson’s disease

Parkinson’s disease (PD) is a progressive move-
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ment disorder characterized by degeneration of dopaminergic neurons in the substantia nigra and their terminals in striatum. This neuronal loss leads to motor symptoms such as resting tremor, slowness of movement, rigidity and bradykinesia. A common pathomorphological feature of PD is the presence of Lewy bodies, whose are abnormal aggregates of alpha-synuclein found not only in nigrostriatal neurons, but widely distributed in the CNS (Moore et al., 2005).

Likewise a number of neurodegenerative diseases, PD is also characterized by microglial activation, which contribute to neuronal death through oxidative stress and increased cytokines production (Chung et al., 2010). It has been shown that pro-inflammatory mediators such as cyclooxygenase 2 (COX2) and the cytokines IL-1β, IL-6, TNF-α and transforming growth factor-α (TGF-α) are increased in postmortem brain of PD patients (Mogi et al., 1994; Nagatsu et al., 2000; Teismann et al., 2003; Nagatsu e Sawada, 2007). Besides the neuroinflammation, there is a systemic inflammatory response resulting in higher levels of IL-1, IL-6 and TNF-α, as demonstrated in peripheral blood mononuclear cells and in serum of PD patients (Bessler et al., 1999; Brodacki et al., 2008; Reale et al., 2009). Additionally, it has been suggested that inflammation might be a causative factor for PD. Koprich et al. (Koprich et al., 2008) demonstrated that LPS treatment into the substantia nigra induces a massive inflammatory response in the brain and predispose dopaminergic neurons to be more vulnerable to death in an animal model of PD. Thus, preexisting inflammation in the brain could increase the risk to develop the disease.

The transcriptional factor NfκB is also involved in the pathophysiology of PD. It was found an increase in NfκB expression in astrocytes, microglia and neuronal cells both in patients and in mice with PD (Ghosh et al., 2007). After administration of N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), a neurotoxin that promotes selective destruction of dopaminergic neurons and simulate symptoms of PD, it was demonstrated an upregulation of Bcl-2 in the ventral midbrain. However, Bcl-2 seems to be phosphorylated after MPTP, which impairs its anti-apoptotic function (Karanakaran e Ravindranath, 2009). Thus, therapies involving modulation of anti-apoptotic proteins such as Bcl-2 could benefit PD treatment. Rasagiline is an inhibitor of monoamine oxidase and it has been shown to protect animal models of PD and also patients from the usual symptomatology (Leegwater-Kim e Bortan, 2010). It is not well defined whether rasagiline mechanism of action is through NFkB pathway, however, it has been demonstrated that rasagiline treatment increases Bcl-2 gene expression (Youdim, 2003).

Another potential therapeutic tool in PD is the employment of neural stem cells. Beyond all the ethical discussion on this issue, there are substantial limitations in terms of how the transplanted cells could differentiate properly and make suitable synaptic contacts. However, it has been shown that after neural stem cells transplantation, Bcl-XL, a Bcl-2 family member, enhances the maintenance of dopaminergic neurons and protects cells from apoptosis during differentiation in vitro and in an in vivo model of PD (Courtois et al., 2010). In addition, Nurr1, which is a transcriptional factor that belongs to the nuclear receptor (NR)4 family of orphan nuclear receptor, has been described as an important player in PD. Nurr1 is able to drive dopaminergic neuron differentiation in vitro together with other transcriptional factors. Also, it was demonstrated that transplantation of neural stem cells transduced with Nurr1 and Foxa2 significantly reversed motor deficits in a rat PD model (Lee et al., 2010). Furthermore, it was shown that Nurr1 inhibits the expression of pro-inflammatory mediators in both microglia and astrocytes and reduced expression of Nurr1 leads to increased inflammatory responses in glial cells causing loss of dopaminergic neurons. A plausible mechanism for this anti-inflammatory function of Nurr1 is through its association to NFκB in order to repress inflammatory genes promoters (Saijo et al., 2009). Thus, NFκB activation in PD should be thinly regulated since it leads to upregulation of protective molecules, such as Bcl-2 and Bcl-XL and noxious pro-inflammatory mediators as well.

The involvement of HO-1 in PD has been considered in several studies. However, whether it is a protective or harmful agent is not well defined. Hung et al. (Hung et al., 2008) had shown that overexpression of HO-1 improved the survival rate of dopaminergic neurons by reducing the production of TNF-α and IL-1b in the substantia nigra and also by increasing neurotrophic factors expression. On the other hand, it is des-
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cribed that Lewy bodies in the substantia nigra present intense HO-1 immunoreactivity, which is associated with high levels of oxidative stress by iron deposition (Schipper et al., 1998). However, HO-1 knockout mice have not shown striking differences between their wild type littermates in dopaminergic degeneration in response to MPTP (Innamorato et al., 2010). Further studies are necessary to find out the precise role of HO-1 in neurodegenerative disorders.

Stroke

Stroke is the third leading cause of morbidity and mortality in adults, accounting for about 2–4% of total health-care costs. According to the World Health Organization, 15 million people suffer stroke worldwide each year. Of these, 5 million die and another 5 million are permanently disable (Cope e Allison, 2008; Donnan et al., 2008). Acute ischemic stroke results from sudden decrease or loss of blood circulation to an area of the brain, resulting in a corresponding loss of neurological function (Donnan et al., 2008). The series of neurochemical processes that are unleashed by focal ischemia can be summarized as cellular bioenergetic failure due to focal cerebral hypoperfusion, followed by excitotoxicity oxidative stress, blood-brain barriers dysfunction, microvascular injury, hemostatic activation, post-ischemic inflammation and finally cell death. Although reperfusion is critical for restoring the normal cerebral function, after restoration of blood circulation, cerebral injury continues over hours or even days (Zivin, 1998). While cells in the ischemic core are killed rapidly, cells in the ischemic penumbra, a region of functionally impaired but structurally intact tissue that lies between the lethally damaged core and the normal brain, subsist due to ongoing ischemic injury, resulting in expansion of the infarcted core. Since salvage of this tissue is associated with neurological improvement and recovery, it is the target for the acute stroke therapy (Obrenovitch, 1995; Back, 1998). Ongoing developments in acute stroke therapy mainly focus on restoration of cerebral perfusion and neuroprotection.

Accumulating evidence suggests that inflammatory reactions are involved in the secondary neurodegeneration in the peri-infarct tissue following stroke. The hallmark of the inflammatory response in the brain is leucocyte infiltration, a blood-brain-barrier (BBB)-mediated event, in which the release of cytokines such as IL1b, IL-6 and TNF-a by activated microglial cells are initiators. These proinflammatory mediators activate vascular endothelial cells, promoting the expression of adhesion molecules and leucocytes migration across the BBB into the extravascular space, where they may initiate microvascular plugging, stasis and thrombosis (Stanimirovic e Satoh, 2000; Bauer et al., 2001). NFkB directly regulates the induction of inflammatory cytokines such as IL1b, TNF-a and IL-6 as well as adhesion molecules E-selectin, ICAM-1 and VCAM-1 (Baeuerle e Henkel, 1994).

TNF-a is crucially involved in the initiation, progression and regeneration after stroke. While blockade of TNF-a action reduces the area of infarct and neurological deficits, knockout mice for TNF receptor demonstrate dramatic exacerbation of neuronal damage in stroke, suggesting that early endogenous TNF-a release after insult is neuroprotective (Nawashiro et al., 1997a; b; c; Turrin e Rivest, 2006). These findings point for a dual role of TNF-a as a deleterious and yet protective cytokine (Sairanen et al., 2001). Many signaling molecules and anti-apoptotic effectors, such as Bcl-2, Bcl-xL and A20, can be induced by TNF, contributing for its neuroprotective function (Tarkowski et al., 1997).

The Bcl-2 family proteins play an important role in the regulation of neuron survival during brain ischemia. Among those, the anti-apoptotic Bcl-2 family members Bcl-2 and Bcl-xL and the BH3-only proapoptotic proteins Bim and Noxa are significantly induced after transient brain ischemia. Experimental animals models have shown that increased expression of Bcl-2 and Bcl-xL correlated to decreased infarct area. Bcl-2 has been shown to protect neurons from stroke damage by preventing pore formation and cytochrome c release from the mitochondria and the generation of subsequent signals that will lead to cell death and appears to play a key role in models of induced tolerance to focal ischemia (Davies et al., 2000; Liu et al., 2009). In fact, several compounds such as 4-hydroxybenzyl alcohol (Yu et al., 2010), lycopene (Wei, Shen et al., 2010) and dauricine (Yang, Liu et al., 2010) and delta-opioid receptor (Ma, Qian et al., 2005) show neuroprotective effects against cerebral ischemia via induction of Bcl-2 expression.
It is still unknown how A20 levels change in the brain during the course of stroke. However, A20 overexpression via intrathecal gene transfer reduced the infarct volume probably by limiting neuronal apoptosis in the penumbral zone in a rat model of focal ischemia indicating a neuroprotective function of A20 on ischemic damage (Yu, Miao et al., 2006).

HO-1 has a strong neuroprotective effect after stroke has been demonstrated. HO-1 expression was increased in response to resveratrol treatment, a potent antioxidant, reducing infarct area in the brain following middle cerebral artery occlusion and this effect was prevented in HO-1 knockout mice (Sakata, Zhuang et al., 2010). After treatment with epicatechin, a polyphenol antioxidant as resveratrol, less neurodegeneration was found after stroke, and this protective effect was lost in HO-1 knockout mice (Shah, Li et al., 2010). Thus, antioxidants pathways require HO-1 expression in order to promote protection in the CNS after hypoxic-ischemic injury.

**Concluding remarks**

Neuroinflammation is a common response to a variety of damaging stimuli in the CNS. It is an important event in the pathogenesis of progressive neurodegenerative disorders, such as AD and PD and also plays a crucial role in the development of the damage following stroke. Thus, therapies aiming to prevent or block neuroinflammation would be helpful to limit brain damage in these pathological conditions. Currently, there are some reports showing decrease in amyloid deposition in AD after non-steroidal anti-inflammatory drugs (NSAIDs) therapy. However, selective inhibitors of COX-1/COX-2 have not shown promising results (Heneka, O’banion et al., 2010). Classical pro-inflammatory targets have not shown full protection in neuroinflammation (Davies, Reddy et al., 2000; Liu, Sheng et al., 2009). The inflammatory pathways involve intricate interactions as it is evident in the NFkB cascade, for example: inflammatory stimuli induce NFkB activation, which in turn modifies gene expression of protective and harmful mediators whose participate in inflammatory responses and also modulate cell survival and apoptosis. A20, for example, is well described as a potent cytoprotective molecule in a number of cell types and experimental models, however its role in the CNS remains to be elucidated. In spite of a lack of studies, A20 seems to be a reasonable candidate as an anti-inflammatory molecule in the brain and, consequently as a neuroprotective agent. Thus, modulation of NFkB pathway certainly would be a valuable target to prevent neurodegeneration/neuroinflammation. More studies are needed to establish the precise role of inflammatory molecules in neurodegeneration and to develop more successful therapy tools.
### Abbreviations:

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<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AD</td>
<td>Alzheimer's disease</td>
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<tr>
<td>BBB</td>
<td>blood-brain-barrier</td>
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<td>Bcl-2</td>
<td>B-cell lymphoma 2</td>
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<td>Bcl-XL</td>
<td>B-cell lymphoma extra large</td>
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<td>CNS</td>
<td>central nervous system</td>
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<td>COX1</td>
<td>cyclooxygenase 1</td>
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<td>COX2</td>
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<td>HO-1</td>
<td>heme-oxygenase 1</td>
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<td>ICAM-1</td>
<td>intercellular adhesion molecule 1</td>
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<td>IκB-a</td>
<td>inhibitory protein kappa B</td>
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<td>IκB kinase</td>
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<td>Interleukin-6</td>
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<td>iNOS</td>
<td>inducible nitric oxide synthase</td>
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<td>LPS</td>
<td>lipopolysaccharide</td>
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<td>mACHR</td>
<td>muscarinic acetylcholine receptors</td>
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<td>MCP-1</td>
<td>monocyte chemoattractant protein 1</td>
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<td>MIP-1α</td>
<td>macrophage inflammatory peptide-1alpha</td>
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<td>MPTP</td>
<td>N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine</td>
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<td>NFκB</td>
<td>Nuclear transcription factor kappa B</td>
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<td>PD</td>
<td>Parkinson's disease</td>
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<td>TNF-α</td>
<td>tumor necrosis factor-α</td>
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<td>TNFR1</td>
<td>tumor necrosis factor receptor 1</td>
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<td>TGF-α</td>
<td>transforming growth factor-α</td>
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<tr>
<td>VCAM-1</td>
<td>vascular cell adhesion molecule 1</td>
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