

Review Article:

THE ROLE OF MICROGLIA AS PRIME COMPONENT OF CNS IMMUNE SYSTEM IN ACUTE AND CHRONIC NEUROINFLAMMATION

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ABSTRACT

The understanding of microglia function in central nervous system (CNS) immune system has changed the neuroscientists' view on CNS response to activating stimuli. Once microglia were considered a supporting cell, in the last 2 decades however they have been recognized as the prime component of CNS immune system due to their ability to actively response to both acute and chronic/persistent stimuli by proliferation and production of pro-inflammatory cytokines and other toxic substances. Many studies have shown that pro-inflammatory cytokines produced by microglia play role in secondary CNS injury. Many other studies however have established that potentially toxic mediators (e.g. glutamate, Ca²⁺ and reactive oxygen species/ROS) released in traumatic CNS injury play prominent role in secondary CNS injury. We think therefore that the role of pro-inflammatory cytokines in secondary CNS injury is uncertain. This uncertainty is supported by the finding that pro-inflammatory cytokines affect only damaged neurons, which are caused by those potentially toxic mediators. The dual inflammatory response of cytokines also supports this uncertainty. On the basis of the above findings, we therefore suggest studies investigating the role of microglia in contributing secondary CNS injury and the effectiveness of suppressing microglia response to produce toxic substances to improve the outcome of CNS injured patients should be carried out. It has been proposed that neuroinflammation proceeds neuronal loss in many neurological disorders such in Alzheimer's disease (AD). Non-steroid anti-inflammation drugs (NSAIDs) therefore have been widely used in the management of AD. Many studies however have shown that NSAIDs are not effective to suppress the progressive neuronal loss in AD. Looking at the responsible of microglia (neuroinflammation) in neuronal loss and the failure of NSAIDs in improving outcomes of AD patients, we therefore hypothesize that suppressing microglia response to produce toxic substances may account for reducing neuronal loss in AD.

Keywords: neuroinflammation, microglia, cytokines

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INTRODUCTION

The presence of barrier that limits peripheral cells and protein substances enter and function and the absence of lymphatic system, which can catch potential antigen and produce T and B lymphocytes make central nervous system (CNS) as a privileged immune organ (Layé et al. 1999). Consequently, CNS must have its own immune system. Microglia, once were considered as a supporting cell in CNS tissue (Jessen 2004), in the last 2 decades however they have been recognized as prime component of CNS immune system due to their ability to be activated in the presence of activating stimuli (Carbonell et al. 2005; Giulian 1999; Streit et al. 2004). This activated microglia has capability to migrate and phagocytize the injury agents and produce pro-inflammatory cytokines such as IL-1 β , IL-6 and TNF- α (Layé et al. 1999; Streit et al. 1998; Yang et al. 2004)

that are able to injure neuron (Yang et al., 2004). The response of activated microglia is analogous to the response of activated immune cell in periphery (Streit et al. 2004).

Before the recognition of prominent role of microglia in CNS immune system, neuroscientists used "reactive gliosis" term to describe the passive response of microglia to acute injury agent (Streit et al. 2004). This response is characterized by the presence of enlarged glial cell such as microglia and astroglia in the injured site. They now use "neuroinflammation" term to demonstrate the active response of microglia to activating stimuli, which is characterized by the presence pro-inflammatory cytokines and other toxic substance produced by activated microglia (Streit et al. 2004).

Neuritic and glial changes associated with the extracellular amyloid fibrils (plaque) in many neurological disorders such in Alzheimer's disease (AD) and Prion disease (PD) were considered a passive reaction of brain tissue to a foreign substance (Eikelenboom et al. 2002). The rapid understanding of microglia as prime component in CNS immune system has changed the view of neuroscientists to these changes (Streit et al. 2004). These changes now are recognized as CNS inflammatory response, which is characterized by the presence of cluster of activated microglia and activated complement factors (Akiyama et al. 2000; Giulian 1999; Eikelenboom et al. 2002; Koistinaho & Koistinaho 2005; McGeer & McGeer 2002; Streit 2004; Rothwell et al. 1997).

Since the critical role of microglia in CNS injury, they therefore have been proposed as a key cellular mediator in inflammatory processes both in acute and chronic inflammation (Carbonell et al. 2005; Layé et al. 1999; Streit et al. 2004). Many studies have shown the role of pro-inflammatory cytokines (e.g. IL-1 β , IL-6 and TNF- α) produced by microglia in secondary CNS injury. Many other studies however have established that potentially toxic mediator (e.g. glutamate, Ca²⁺ and ROS) released in traumatic CNS injury play critical role in secondary brain injury (Bayir et al. 2002; Hall 1991). Looking at the critical role of these potentially toxic mediators in the cascade event of secondary CNS injury, we therefore think that the role of pro-inflammatory cytokines produced by microglia in secondary CNS injury is uncertain.

It has been proposed that inflammation precedes neuronal damage (neurodegeneration) in AD. Many studies have shown that plaque itself cannot cause neuronal damage (Giulian 1999). However, amyloid plaque that contains various substances can stimulate microglia to produce neurotoxic substances such as cytokines, excitotoxin, nitrite oxide and lipophylic amines, which cause neural damage (Giulian 1999). Thus tissue injury in AD may depend therefore in the magnitude of microglia response to senile plaque, not simply on plaque density (Eikelenboom et al. 2002; Giulian 1999). NSAIDs that are very commonly used in the management of AD do not effectively improve the clinical course of AD patients (Eikelenboom et al. 2002; Giulian 1999). Looking at the main role of microglia in tissue injury and the failure of NSAID in improving clinical outcomes, we therefore hypothesize that suppressing microglia response to produce potentially toxic substances could account for reducing neural damage, hence improves the clinical outcomes of AD patients.

This review gives a new understanding of microglia function in acute and chronic CNS inflammation. Although many studies have shown the role of microglia in cascade event of CNS injury, it is still uncertain however. The current management of head injury therefore has not been changed yet. The understanding of chronic CNS inflammation in neurodegeneration results in the common use of NSAID to prevent progressive dementia in AD patients. Many studies however have failed to show the effectiveness of these drugs to improve the outcome of AD patients. Further works therefore should be carried out to find out a better substance to deter progressive neuronal loss in AD brain.

DISCUSSION

Possible Role of Microglia in Secondary CNS Injury

Traumatic CNS injury is an acute inflammation (Ghinikar et al. 1998; Lenzlinger et al. 2001; Smith et al. 2003; Sroga et al. 2003; Streit et al. 2004; Yang et al. 2004), because it produces wide variety of protein such as beta amyloid precursor protein and its products and amyloid beta (A β) peptides neurofilament protein (Babcock et al. 2003; Smith et al. 2003), which cause an immediate and early response of living brain tissue to injury (Streit et al. 2004). This response is characterized by the presence of activated microglia stimulated by the above proteins. Many studies have shown the role of microglia as a sensor in CNS injury. Streit et al. 1998 revealed that endogenous glial cells mainly microglia not the peripheral immune cells are responsible for the production of cytokines such IL-1 β , IL-6 and TNF- α . Herx et al. 2000 showed that there is an increase in IL-1 β production 15 minutes after head injury in mice, and it is followed by the increase of IL-1 α and TNF- α production in the next one hour. In this experimental study, they revealed that microglia, not leukocytes, is to be the sole source of these cytokines production. Yang et al. 2004 demonstrated the role of intrinsic immune cells (e.g. microglia, astroglia) in cascade events of CNS injury. They showed that 0.5 hours following spinal cord injury the production of pro-inflammatory cytokines are significantly increase without the presence of peripheral cells such as neutrophil and macrophage. They concluded endogenous cells (microglia, astroglia and neuron) not peripheral cells play a critical role in the initiation and propagation of early posttraumatic inflammatory response by producing pro-inflammatory cytokines.

Many studies have shown cytokines such as IL-1 β , IL-6 and TNF- α are inflammatory mediators and may play role in cascade event of CNS injury (Foster-Barber et al.

2001; Ghinikar et al. 1998; Herx et al. 2000; Klusman & Schwab 1997; Rothwell et al. 1997; Yang et al. 2004). The role of IL-1 β in secondary CNS injury has been shown that IL-1 β receptor antagonist (IL-1ra) attenuates neural damage in experimental traumatic CNS injury (Herx et al. 2000; Rothwell et al. 1997; Toulmond et al. 1995). Similarly, IL-6 has prominent role in the pathobiology of traumatic CNS injury. IL-6 deficient mice showed defective in the inflammatory response, e.g. reduced activity of microglia (Hans et al. 1999). TNF- α , a multifunctional cytokine also play role in the cascade event of traumatic CNS injury. Antagonist of TNF- α attenuates neural degeneration in experimental head injury (Shohami et al. 1996).

The above studies have shown the role of pro-inflammatory cytokines produced by microglia in secondary CNS injury. Many other studies however have established that potentially toxic mediators (e.g. glutamate, Ca²⁺ and ROS) released in traumatic CNS injury play prominent role in secondary CNS injury (Bayir et al. 2002). In clinic, therefore substances that can suppress the bad effect of those mediators have been developed and widely used to improve the outcomes of head injured patients (Bayir et al. 2002; Hall 1991). Thus the role of pro-inflammatory cytokines in secondary CNS injury is uncertain. This is supported by many findings. The bad effects of cytokines need an interaction with other molecules (e.g. glutamate) released in traumatic CNS injury or cytokines affect only compromised tissue, which are most likely caused by extracellular glutamate accumulation, increased Ca²⁺ cytosol and increased ROS production (Allan & Rothwell 2001; Rothwell 1997; Jiyeon et al. 2005). The dual inflammatory response of cytokines may also support this uncertainty (Lenzlinger et al. 2001). On one hand, cytokines are neurotoxic on the other hand they are neuroprotective. These properties of cytokines may prevent the use of anti inflammatory agents to improve clinical outcome of head injured patients.

The Role of Microglia in Neurodegeneration

Chronic inflammation may more relevant in understanding CNS disease, because chronicity implies disease (Streit et al. 2004). Since glia has been recognized a prime component in intrinsic CNS immune system, many neurological disorders are considered as an inflammatory process (Eikelenboom et al. 2002; McGeer & McGeer 2002; Streit et al. 2004; Streit 2004). In multiple sclerosis, inflammation is caused by myelin-related protein that has escaped self-tolerance and become an autoimmunogen. This autoimmunogen is a persistent stimulus that activates microglia (Eikelenboom et al. 2002). This activated microglia damage neuron. Dementia in HIV patient (HIV-

associated dementia) is caused by a nidus that has changed microglia physiology and a changing their physiology causes neuronal damage (Garden 2002).

The recognition of microglia as prime component in CNS immune system is also implied in Alzheimer's disease (AD) and Prion disease (PD). The inflammation in AD and PD are characterized neuropathologically by extracellular deposit of amyloid beta (A β) and PrP amyloid fibrils respectively (Eikelenboom et al. 2002). In these neurological diseases, these cerebral amyloid deposits are co-localized with variety of inflammation-related protein (complement factors, acute phase protein, pro-inflammatory cytokines) and cluster of activated microglia. Microglia appears to be the most prominent inflammatory component in both diseases (Eikelenboom et al. 2002; Giulian 1999; McGeer & McGeer 2002). Amyloid beta protein forming insoluble and pathological extracellular aggregates (foreign substance) may serve as a stable irritant that hold the CNS in chronic states by continually activating microglia (Akiyama et al. 2000; Giulian 1999; Streit et al. 2004). Clinicopathological and neuroradiological studies have shown that activation of microglia is a relatively early pathogenic event that precedes the process of neurophil destruction (Akiyama et al. 2000; Giulian 1999; Eikelenboom et al. 2002). Activated microglia, therefore, are recognized as the center of the pathogenesis of AD, because they are neurotoxin-producing immune effector cells actively involved in leading to the neurodegeneration or dementia (Giulian 1999; Koistinaho & Koistinaho 2005; Streit 2004). Thus tissue injury in AD may depend on the magnitude of microglia response to amyloid plaque and not simply on plaque density (Giulian 1999). This is shown in a study that plaque itself does not cause neutrophil destruction (Giulian 1999).

The concept that A β can induce local inflammatory response has been proven further. A β can bind complement factor C1, and then it potentially activates classical component pathway (Eikelenboom et al. 2002; McGeer & McGeer 2002). Early activation of this complement may play an important role in the recruitment and activation of local microglia expressing complement receptor CR3 and CR4 (Eikelenboom et al. 2002). Genetic (Graham et al. 1999) and environmental factors (Eikelenboom et al. 2002; Koistinaho & Koistinaho 2005; Rothwell et al. 1997; Streit et al. 2004) are considered to be the causes of AD. Genetic studies have shown inflammation plays role in AD. This is proven by the finding that polymorphism of some plaque-associated pro-inflammatory cytokines (i.e. IL-1 β , IL-6 and TNF- α) are genetic risk factor for AD (Eikelenboom et al. 2002). Repeated head injury and brain ischemia are among the environmental factors in

AD (Eikelenboom et al. 2002; Koistinaho & Koistinaho 2005; Rothwell et al. 1997; Streit et al. 2004.). Animal studies have demonstrated that repeatedly injured brain tissue results in over-expression of β -amyloid precursor protein (APP), precursor of A β (Eikelenboom et al. 2002; Streit et al. 2004). An experimental study has shown that direct amyloid injection into brain tissue activates microglia and an activating microglia reduces the number of neuron (Eikelenboom et al. 2002; Streit et al. 2004). Another advanced experimental study also has shown that transgenic rat expressing APP causes amyloid deposition and neuron injury (Koistinaho & Koistinaho 2005). The pathogenesis of AD is a vicious cycle (Eikelenboom et al. 2002; Rothwell et al. 1997). Amyloid protein activates microglia to produce cytokines especially IL-1 and this cytokine increases amyloid synthesis. This amyloid then re-activates microglia to produce IL-1 and other potentially toxic substances that are able to injure the adjacent neurons (Eikelenboom et al. 2002).

Implication of AD Treatment

Since neuroinflammation plays prominent role in neuronal loss in AD, NSAIDs have been widely used in the management of AD (Akiyama et al. 2000; McGeer & McGeer 2002). Epidemiological studies have shown people consuming NSAIDs because of osteoarthritis or rheumatoid arthritis have lower risk to develop AD (McGeer & McGeer 2002). Many clinical studies however have failed to show the effectiveness of NSAID to prevent progressive neurodegeneration (Eikelenboom et al. 2002; Giulian 1999; Koistinaho & Koistinaho 2005). Administration of IL-1 receptor antagonist (IL-1 ra) in an experimental study also has failed to reduce neurodegeneration in AD (Rothwell et al. 1997). The ineffectiveness of NSAIDs to prevent progressive neurodegeneration may be due to the advance of the disease when it is clinically manifested.

SUMMARY

Brain as a privileged immune organ has been well established. However the role of microglia as prime component of CNS immune system was recognized in the last 2 decades. This prominent role of microglia in CNS immune system has changed neuroscientist's view that CNS response to activating stimuli is an inflammation. Because it does not involved systemic immune response, therefore it is called neuroinflammation. Both acute and chronic inflammation show the prominent microglia role in these inflammations, which is characterized by the presence of activated microglia producing proinflammatory cytokines and other toxic substances.

Acute neuroinflammation is immediate and early response of CNS to injury. Chronic neuroinflammation is a result of permanent stimulation of living tissue to activating stimuli. Chronic neuroinflammation implies disease such as AD, PD and multiple sclerosis.

Many studies have shown the role of pro-inflammatory cytokines in secondary CNS injury. However many studies also have established the role of potentially toxic mediators (e.g. glutamate, Ca²⁺ and ROS) in secondary CNS injury. It is therefore we think that the role of pro-inflammatory cytokines in secondary CNS injury is uncertain. This is supported by the finding that the bad effects of cytokines work only on the damaged neuron, which is most likely caused by potentially toxic mediators. The dual function of cytokine may also support this uncertainty.

It has been recognized that neuroinflammation precedes the neurophil destruction in many neurological disorder such as AD. NSAIDs therefore have been widely used in the management of AD patients. However many studies have shown the ineffectiveness of these drugs to reduce neural loss. An experimental study also has shown the failure of IL-1ra antagonist in suppressing the progressive neuronal loss in AD. Looking at the above findings we therefore hypothesize that suppressing microglia response to produce toxic substance may account for the reducing neural loss in AD brain.

On the basis of our critical literatures review we propose some suggestions: 1) carry out studies investigating the contribution of microglia through their pro-inflammatory cytokines in secondary CNS injury and the effectiveness of suppressing microglia response to activating stimuli to reduce secondary CNS injury. This study is important, because drugs that have been used in traumatic CNS injury do not significantly improve the outcome of head injured patients; 2) carry out a study investigating the effectiveness of suppressing microglia response to produce toxic substances in improving clinical outcomes of patient with AD. This study is also important, regarding the failure of NSAIDs in improving clinical outcomes of AD patients.

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