Microglia and Parkinson's disease*★

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Abstract

BACKGROUND: Because dopaminergic neurons are particularly sensitive to oxidative stress, microglia is characteristics of being prone to activation, and activated microglia is the main source of oxygen free radical production, so microglia activation is more important in the pathogenesis of Parkinson's disease and illness progress.

OBJECTIVE: To summarize the correlation between microglia and Parkinson's disease.

METHODS: An online computer-based retrieval was performed by the first author among the Chinese Journal Full-Text Database (CNKI: 2000/2010) and Medline (2000/2010) Database, with key words of "Parkinson's disease, microglia" in English and Chinese. The correlation between microglia and Parkinson's disease was discussed through two aspects, one is the influence of cell factors and toxic substance produced after microglia activation on Parkinson's disease, the other is the inhibition of microglia and prevention of nerve toxic factors on Parkinson's disease progress.

RESULTS AND CONCLUSION: A total of 112 articles were screened out according to inclusion and exclusion criteria, and 27 of them were involved in the analysis. Results showed that microglia activation will damage dopaminergic neurons, and cause Parkinson's disease. And the occurrence and development of Parkinson's disease may further reduce the neurotransmitter dopamine, continue to damage dopaminergic neurons and release the inflammatory factor, thus promoting microglia activation. Inhibition of microglia activation is likely to stop the progress of Parkinson's disease.

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INTRODUCTION

Parkinson's disease (PD) is a common geriatric neurodegenerative disease, which is mainly pathologically characteristic of the progressive degeneration of nigrostriatal dopaminergic neurons in midbrain and nerve endings. Clinical symptoms include resting tremor, rigidity and bradykinesia[1]. PD incidence is only lower than that of Alzheimer's disease, although individual gene mutations have been linked to some familial PD, the vast majority of PD etiology and pathogenesis remains unclear, therefore PD treatment maintains at the symptomatic level, and there is no completely effective therapeutic measure[2].

With advanced progress of PD pathogenesis research, nerve inflammation particularly microglia activation attracts more and more attention in the degeneration of dopaminergic neurons. McGeer *et al* [3] in 1988 have found activated microglial cells in mesencephalic substantia nigra of PD patients, then scholars are interested in the activation of microglia as the mechanism underlying neural immune inflammation. This study aimed to explore the correlation between microglial activation and PD pathogenesis.

DATA AND METHODS

Information retrieval

An online computer-based retrieval was performed by the first author among the Chinese Journal Full-Text Database (CNKI: 2000/2010) and Medline (2000/2010) Database, with key words of "Parkinson's disease, microglia" in English and Chinese.

Inclusion criteria

(1) Original studies addressing the correlation between PD progress and microglia with reliable argument and evidence. (2) Clear analysis of the influence microglia on PD. (3) Study topic is microglial activation or inhibition mechanism.

Quality evaluation

A total of 112 articles were screened out according to inclusion and exclusion criteria, and 27 articles were involved in the analysis[1-27]. The correlation between microglia and PD was discussed through two aspects, one is the influence of cell factors and toxic substance produced after microglia activation on PD, the other is the inhibition of microglia and prevention of neurotoxic factors on PD progress.

Data extraction

Research contents were extracted by three physicians independently and a discussion was suggested to resolve differences. Information recording focused on microglial activation and inhibition of the activation.

COMPREHENSIVE EVALUATION OF DOCUMENT EVIDENCE

General conditions of involved papers

The involved papers mainly introduced the

distribution and biological characteristics of microglial cells[3-8], neuronal injury activation on microglia[9-14], microglia toxicity on neurons[15-20] and correlation between microglial cells and PD[21-27].

Research features of involved papers

Microglial cells are the main immune cells in the brain, and are not evenly distributed in normal brain, most dense in substantia nigra compacta of the midbrain. Under normal circumstances, microglial cells as static, but they can be transformed into activation and exhibit phagocytic function when mediated by signal stimulation. On one hand, activated microglia releases neurotrophic factors and anti-inflammatory cytokines to play a protective role; on the other hand, microglia activation generates a large amount of free radicals such as superoxide (O^{2-}), intracellular reactive oxygen species, hydrogen peroxide, hydroxyl radical and cytotoxic cytokines, including interleukin 1 beta and tumor necrosis factor alpha, these radicals may injury neurons. An increasing number of studies suggest that dopaminergic neurons are particularly sensitive to oxidative stress, and activated microglial cells are the main source of oxygen free radicals generation. Therefore, microglial cells activated under some nerve growth factors' stimulation can lead to dopaminergic neurons injury. Neuronal damage is irreversible, injured neurons release inflammatory factors to further stimulate microglial cells activation, thereby injuring more dopaminergic neurons. Such a "vicious circle" will directly lead to the decrease or loss of dopaminergic neurotransmitter, causing PD.

Microglial cells are the major mediator of neural immuno-inflammation

Microglia origin and distribution: Microglial cells account for 5%−20% of the total number of glial cells, and are the main immune cells in brains. The microglia origin remains unclear, but most scholars believed that they originate from bone marrow precursor cells in mesoderm, that is mononuclear phagocytic system. These cells in the adult period are located in central nervous system interstitial tissue, and become intrinsic glial cells. In normal brains, microglial cells are not evenly distributed, and the density is the maximum in mesencephalic substantia nigra compacta[3-4].

Biological characteristics of microglial cells: Block *et al* [5] reported that microglia is the sensor of central nervous system pathological event. Under normal circumstances, microglial cells are static or toothed, the cell body is small with extending processes. Mediated by signal stimulation, static microglial cells convert to activate without the phagocytic function, the cell bodies enlarges, neurites become shorter, cells are round or rod shaped. Microglial cells continue to transform, cell body is round, cell processes disappear and are amoeba-like shaped, and cells have phagocytosis function, which indicate activation of microglial cells.

Microglial activation and function: Microglial cells are sensitive to environmental stimuli, and can be rapidly activated by certain signal stimulation. When the morphology of microglial cells changes from the static into the activated, the functions also alter, cell surface expressed CR3 complement receptor and the major histocompatibility complex molecules are upregulated, synthesis and secretion of cytokines are facilitated, such as tumor necrosis factor alpha, interleukin 1 beta and interferon gamma, peroxide, nitric oxide. Whether microglial activation plays a neuroprotective role or a toxic injury remains controversial. On one hand, the activated microglial cells release neurotrophic factors and anti-inflammatory cytokines, thus playing a protective role; on the other hand, microglial activation produced lots of free radicals such as superoxide, intracellular reactive oxygen species, hydrogen peroxide, hydroxyl radical and cytotoxic cytokines, including interleukin 1 beta and tumor necrosis factor alpha, thus injuring neurons[6]. Microglial cells has a dual role on neurons, its activation cannot necessarily lead to injury, but excessive activation will have serious consequences, which depends on the stimulator's type and intensity, as well as the body's response to such factors.

Microglia expression marker in the neurons-CD200: A large amount of studies showed that, neurons express CD200 and act in microglial cells CD200R, thus regulating microglial activation. Downregulation of CD200-CD200R signal leads to abnormal activation of microglial cells. CD200 is a cell surface glycoprotein, which belongs to the leukocyte differentiation antigen, CD200 is widely distributed and expressed in a variety of cells, including the activated T cells, B cells, follicular dendritic cells and neurons. CD200R distribution is limited, only in myeloid cells, such as macrophages and mast cells. In the nervous system, CD200R is mainly expressed in microglia[7]. In general, CD200 labels certain tissues (neurons in the nervous system), which have a common feature of transferring regulating signals to myeloid cells (microglia in the nervous system), which express CD200R, thus modulating the activity of these cells and avoiding excessive activation. Many studies have revealed the correlation between CD200-CD200R signaling pathway and neuron-microglial cells[7-8], in addition to the role of microglial cells in PD pathogenesis, future research is required to focus on CD200-CD200R.

Neuronal injury on microglial activation

In various nervous system diseases, the injured and died neurons can activate microglial cells through a

variety of cytokines. Among them, extracellular matrix components, alpha synuclein protein and neuropeptide melanin are the most ones.

Extracellular matrix: Neuronal damage may influence the components of extracellular matrix, thus activating microglial cells and promoting the production of inflammatory factor such as superoxide. Absence or inhibition of microglia and neuronal interaction *via* intercellular adhesion molecule-1 will lead to microglial activation and various toxic factors release[9]. Extracellular matrix proteins, laminin, correlates with MPP^+-induced activation of microglial cells, increase of extracellular peroxidase and dopaminergic neuron injury[10]. In addition, neuronal injury can also release some protein enzyme components which act on extracellular matrix, such as matrix metalloproteinase 3. Therefore, neuronal injury may influence extracellular matrix to provide a chronic neuritis response.

Alpha synuclein protein: Lewy bodies are one kind of PD pathological characteristics, its essence is the filamentous cytoplasmic accumulation containing alpha synuclein protein, and possibly play a key role in PD and other neurodegenerative disease [11]. Extensive evidence suggested that, abnormal accumulation of wild-type or mutant alpha synuclein protein can directly lead to dopaminergic neuronal death [12]. A number of studies have shown that, extracellular Lewy bodies and alpha synuclein protein expression-positive substantia nigra accumulation can be surrounded by microglial cells or various inflammatory mediators; alpha synuclein protein that releases into the extracellular can form accumulation to activate microglial cells, leading to the increase of extracellular superoxide and selective dopaminergic neurons injury[13].

Neurotropic melanin: Neuropeptide melanin is black insoluble macromolecular particulate material with highest content in the dopaminergic neurons of midbrain substantia nigra pars compacta, its accumulation gradually increases with aging in healthy individuals. Melanin has potential toxicity on dopaminergic neurons, excessive dose direct inhibits proteasomal activity. Several studies demonstrate that, melanin is also present around dopaminergic neurons. In young PD, sporadic PD and individuals with 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine-induced Parkinson symptom, melanin is visible. Extracellular melanin can sustained activate microglia, produce a large number of free radicals, cytotoxic cytokines and prostaglandins, which further damage dopaminergic neurons[14].

Neuronal toxic effects of microglial cells are as follows:

(1) Oxidative stress of microglial cells: The activated microglia may generate free radicals, which has neuronal toxicity. Reactive oxygen species include a variety of oxygen free radicals and various non-radical oxygenates which are closely related to free radical behavior. Reactive oxygen species generate cytotoxicity, known as oxidative stress, which can induce polyunsaturated fatty acid lipid peroxidation, and lead to large molecule substances especially DNA changes, also produce cell necrosis and apoptosis[15].

(2) Excitability toxicity of microglial cells: Activated microglial cells can synthesize prostaglandin E2. Prostaglandin E is a medium of cell N-methyl-D-aspartate glutamate receptor postsynaptic signaling cascade. Prostaglandin E inhibits astrocyte and reuptakes glutamate, enhances glutamatergic neurons transfer. Glutamate is an important excitatory neurotransmitter in central nervous system. Under pathological conditions, extracellular glutamate concentration increases, excessive stimulation of the receptor can produce distinct excitatory toxicity on central nervous system, resulting in the degeneration and death of dopaminergic neurons.

(3) Microglial cell immunity and phagocytosis: In PD substantia nigra, microglial activation and phagocytosis of dopaminergic neurons may initiate an effective cell death. Dopamine is the immune response cells in nervous system, with MHC II weak positivity, and can prime immune response in central nervous system. In fact, microglia is the phagocytic cells in nervous system, excessive immune responses, complement activation, antibody dependent cell cytotoxicity and phagocytosis may damage the central nervous system[16].

(4) Cytokine damage of microglia: Microglial cells through interleukin 12P40 to induce nitric oxide synthase and nuclear transcription factor-kappa activation[17-18], activated nuclear transcription factor kappa B can highly induce a variety of cytokines, chemokines, adhesion molecules, immune recognition receptor, acute response protein, inflammatory proteases and other transcription factors, thus generating a plurality of cascade fall amplification effect, and causing inflammation injury and death of dopaminergic neurons. Activated microglial cells can synthesize and release tumor necrosis factor alpha and nitric oxide, interleukin 1 beta, interleukin 6, and other cytotoxic factor. Local sustained increase of cytotoxic factor produces toxic effects on dopaminergic neurons, eventually causing PD. In addition, interferon gamma can not only induce microglial to produce nitric oxide *via* interferon regulatory factor 1, but also induces caspase 11 expression, priming microglial cells is not dependent on nitric oxide cell apoptosis. Interferon regulatory factor 1 and caspase 11 are the essential substances of microglial inducing cell death[19]. Therefore, interferon gamma activation of microglial cells has toxic effects on dopaminergic neurons.

(5) Chemotactic cytokines and adhesion molecules of microglial cells: The activated microglial cells can

produce chemokines such as cytokine induced neutrophil chemoattractant factor, monocyte chemoattractant protein1, macrophage inflammatory protein 1 and adhesion molecules, including intercellular adhesion molecule 1, endothelial cells adhesion molecules, and p-selectin. In PD and other chronic degenerative diseases, microglial cells sustained produce chemokines and adhesion molecules, which can damage the neurons. In central nervous system, extracellular matrix protein tenascin-R against microglial cell adhesion, have a neuroprotective effect[20]. Chemotactic cytokines and adhesion molecules are not the main factor in PD process, but perhaps they promote the action.

Microglia and PD

Under normal circumstances, brain tissue may provide an immunosuppressive environment, to maintain the functions of central nervous system. When the environment is destroyed by chronic inflammation, such as infectious diseases, autoimmune diseases or neurodegenerative diseases, a series of immune response mechanism will be activated. Although a variety of cell types have been proved, including peripheral immune cells, neurons, microglia and astrocytes infiltration into the brain tissue, which are source of cytokines in the central nervous system, studies still show that microglial cells are primary sources of proinflammatory and immunoregulatory cytokines. In various types of neurons in central nervous system, dopaminergic neurons is particularly sensitive to microglial activation, some proinflammatory stimuli, such as lipopolysaccharides on Gram negative bacteria cell wall, can activate microglia to induce selective loss of dopaminergic neurons[21-22]. A number of experimental studies confirm that, microglial activation is the main reason for the death of dopaminergic neurons, such as lipopolysaccharides only exhibits neuronal toxicity effects under the presence of microglia. Both *in vivo* and *in vitro* experiments showed that lipopolysaccharides can activate microglia and cause the death of dopaminergic neurons.

PD is a common degenerative diseases in central nervous system, its main pathological features are degeneration and necrosis of dopaminergic neurons in substantia nigra compacta. Mirza *et al* [23] found that dopaminergic neuron loss is accompanied by distinct glial cell reaction in autopsy of PD patients. The activation of microglia is great, glial expressing proinflammatory cytokines such as tumor necrosis factor alpha and interleukin 1 beta are increased. Ouchi *et al* [24] demonstrated that, the number of activated microglial cell increased obviously in early PD patients by positron emission tomography, and accompanied by the loss of dopaminergic neurons. The experimental findings suggest that endogenous microglia induced inflammatory has significant influence on degenerative disease progression. Microglial cells are at a quiescent state in normal brain, after activation, it could up-regulate levels of various receptors and other molecules in inflammation or phagocytosis. The activated microglial cells can release a large number of pro-inflammatory cytokines (tumor necrosis factor alpha and interleukin 1 beta), nitric oxide, reactive oxygen metabolites and other substances, which have toxic effects on neurons. Interleukin 1 beta and tumor necrosis factor alpha are two major proinflammatory cytokine produced by microglia in the central nervous system inflammation. Lipopolysaccharide can instantly induce an increasing production of interleukin 1 beta and tumor necrosis factor alpha in microglia[25]. Cultured microglia exhibits neurotoxicity effects, including damage to dopaminergic cells. In sporadic and familial PD, there are numerous reactive microglial cells. The presence of activated microglia in human mesencephalic substantia nigra and the death of monkeys exposed to MPTP for several years have proved long-standing inflammation in PD process.

In preliminary studies of Wang *et al* [26], after microglial activation agent lipopolysaccharide was injected into different regions of human brains, dopaminergic neurons in midbrain was sensitive to the neurotoxicity, accompanied by obvious microglial reaction, so lipopolysaccharide injected into the substantia nigra can be used as the ideal model for studying the influence of inflammatory response on the dopamine system. In addition, Zheng and Hwang *et al* [27] used lipopolysaccharide to culture rat midbrain neurons-glial cells in *in vitro* experiments, and results found that microglia was activated and released cytokines (tumor necrosis factor alpha, interleukin 1 beta) and nitric oxide, thus leading to degeneration and necrosis of dopaminergic neurons. Another studies have demonstrated that astrocytes can enhance the MPTP and 6-OH dopamine-induced toxicity on cultured neurons, which indicate that altered function of microglia is one of the pathways for promoting dopaminergic neuronal death.

Above researches confirm that, microglial activation plays a vicious role in PD pathogenesis among PD patients, animal models and *in vitro* experiments, although it is still unclear that whether microglial activation is the primary event associated with the degeneration and death of dopaminergic neurons in the substantia nigral of PD patients, or secondary to neuronal death. Strong evidence suggest that microglial cells is involved in PD denaturation process, which provides new ideas for PD pathogenesis

research and better treatment–inhibition of microglial activation, reduction of toxic cytokine generation, and slow down the degeneration and death of dopaminergic neurons.

The common measures for the inhibition of microglia activation include non-steroid anti-inflammatory drugs, nuclear transcription factor kappa B inhibitors, and neuropeptide drugs. Experimental results showed that: (1) Non-steroid anti-inflammatory drugs can inhibit microglial synthesis of prostaglandin E2, interleukin 1 beta, and nitric oxide. (2) Neuropeptides inhibit tumor necrosis factor alpha transcription and translation in microglial cells. (3) Nuclear transcription factor kappa B inhibitors: Nuclear transcription factor kappa B is the key transcription factor for microglial activation and cytokine release. (4) Cytokines: Transforming growth factor beta inhibits microglial release of cytotoxic substances, and interleukin 4 suppresses microglial phagocytosis. (5) Prostaglandins: Cyclopentanone prostaglandin inhibits microglial cells generation of cyclo-oxygenase, nitric oxide synthase enzyme, tumor necrosis factor alpha, and interleukin 1 beta; through independent and dependent protein kinase A pathway, prostaglandin E2 inhibits microglial production of tumor necrosis factor alpha and interleukin 6.

SUMMARY

This paper discusses the role of microglial activation played in PD process, and this role is attracting more and more attention. Although some studies suggest that microglial activation induces neural immune inflammatory response to have a protective effect on neurons, excessive activation of microglial cells posses more damage to brain neurons especially the dopaminergic neurons in substantia nigra, than its beneficial effect. An increasing number of studies have shown that, inhibition of the proliferation of glial cells and nitric oxide synthase-induced neuronal degeneration currently represent the most promising treatment for delaying, or even preventing PD process. Therefore, the influence of microglial activation in PD pathogenesis has been further confirmed, inhibition of microglial activation contributes to prevent PD progression, which provide a reliable basis for PD prevention and treatment.

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小胶质细胞与帕金森病*★

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摘要

背景：由于多巴胺能神经元对氧化应激特别敏感，小胶质细胞的重要特点之一是易活化，而活化的小胶质细胞是氧自由基产生的主要来源，因此小胶质细胞的激活在帕金森病的发病和病情进展中具有更加重要的作用。

目的：总结讨论小胶质细胞与帕金森病的相互关系。

方法：由第一作者用计算机检索中国期刊全文数据库(CNKI：2000/2010)和Medline数据库(2000/2010)，检索词分别为“帕金森病，小胶质细胞”和“Parkinson's disease, Microglia”，从小胶质细胞激活后产生的细胞因子、毒性物质对帕金森病发病的影响与抑制小胶质细胞的激活，阻止神经毒性因子的损害作用进而阻止帕金森病的进展2方面进行总结，对小胶质细胞与帕金森病的相互关系作相关介绍。

结果与结论：共检索到112篇文章，按纳入和排除标准对文献进行筛选，共纳入27篇文章。结果表明小胶质细胞的激活会损伤多巴胺能神经元，从而引发帕金森病。而帕金森病的发生发展则使多巴胺递质进一步减少、继续损伤多巴胺能神经元并释放炎性因子促使小胶质细胞激活。抑制小胶质细胞的激活则有可能阻止帕金森病的进展。

关键词：小胶质细胞；帕金森病；细胞因子；多巴胺能神经元；组织构建
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伦理要求：没有与相关伦理道德冲突的内容。

此问题的已知信息：小胶质细胞在帕金森病的发病过程中起着极为重要的作用，但目前关于如何抑制小胶质细胞激活进而阻止帕金森病发病的研究不多。

本综述增加的新信息：目前大量研究发现神经元通过表达CD200作用于小胶质细胞的CD200R，调控小胶质细胞的激活。CD200-CD200R信号下调，则引起小胶质细胞的异常激活。鉴于CD200-CD200R信号通路与神经元-小胶质细胞之间的相互关系以及小胶质细胞在帕金森病发病中作用的阐明，未来研究者有必要把研究的视角转向CD200-CD200R。

临床应用的意义：文章剖析了小胶质细胞与帕金森病的相互关系，为临床更好地研究帕金森病的发病因素以及帕金森病的预防与治疗提供一定的科学依据。

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