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Review

Microglial Effects on Psychiatric Disorders

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ABSTRACT

Microglia are important in the development, homeostasis, and disorders of the central nervous system. Neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, and multiple sclerosis, as well as autism, severe depression, and schizophrenia, have all been related to microglia-derived neuroinflammation. Imaging techniques such as magnetic resonance imaging and positron emission tomography can detect neuroinflammation. The purpose of this review was to examine the role of microglia in neurodegenerative disorders, with a focus on imaging.

Keywords: Central nervous system, magnetic resonance imaging, microglia, neuroinflammatory disorders, positron-emission tomography

Neuroglia are cells that support neurons in the central nervous system (CNS), although they are not stimulated. These cells are usually smaller than neurons and are five to 10 times more numerous. They make up about half of the total volume of the brain and spinal cord. There are four types of neuroglial cells defined as astrocytes, oligodendrocytes, microglia, and ependymal cells.[1]

In 1856, Rudolf Virchow defined glial cells as a collection of cells that differed from other neurons.[2] Subsequently, in 1913, Ramón y Cajal described an apolar cell population.[3,4] In 1919, Pío del Río-Hortega introduced the modern terminology describing glial cells.[5] With the work of Georg Kreutzberg's group in 1968, microglia cells became the focus of neuroscience research.[6]

Microglia play important roles in brain development and the maintenance of homeostasis as well as neuroinflammation and neurodegeneration.[7] Many genetic and molecular studies conducted in the following years revealed the importance of microglia.[8-10] Thanks to the modern real-time imaging methods such as translocator protein-18 kDa (TSPO) positron emission tomography (PET), diffusion magnetic resonance imaging (MRI)[11,12], microglia have been found to be more active, frequently monitoring brain activity by extending and retracting their processes. In addition, microglia interact with all CNS components and have a significant effect on normal brain functioning and tissue integrity.[13-16] On the other hand, microglial cells play a role in a wide spectrum of diseases and disorders, including infectious diseases (acquired immunodeficiency syndrome (AIDS), human immunodeficiency virus (HIV)), inflammatory-neurodegenerative disorders (Alzheimer's disease, Parkinson's disease, amyotrophic lateral sclerosis, etc.), spinal cord lesions, traumatic brain injury, and psychiatric disorders (schizophrenia).[1,17-21] Here, we aimed to review the effects of microglia on normal brain development and disorders, as well as the diagnosis of microglial cells as imaging, accompanied by the latest technological developments.

MICROGLIA

Embryology

Microglial cells differ from other embryological neuroglial cells and are derived from cells of mesenchymal origin (embryonic yolk sac precursors

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give rise to macrophages outside the nervous system) that invade the CNS late in fetal development.[1,22-24]

It is the smallest of the neuroglial cells and is distributed throughout the CNS. Morphologically, they have small cell bodies that yield numerous spine-like projections and are very similar to connective tissue macrophages. They migrate to the nervous system during fetal life.[1]

Microglia originate from a pool of primitive macrophages from the yolk sac at embryonic day 8.5 in the mouse. At embryonic day 13, microglial precursors can be seen at the base of the 4th ventricle. These cells completely differ from other hematopoietic stem cells and form an independent lineage. In humans, microglial-like cells can be detected at 13 weeks of gestation, while branched microglia can be seen at 21 weeks. Interleukin-34 and DNAX-activating protein of 12 kDa (DAP12) (known as TYRO protein tyrosine kinase-binding protein) and interferon regulatory factor (IRF)-8 deficiency also cause a decrease in microglial density. The colony-stimulating factor-1 (CSF-1) signaling is important for microglia development, and the number of tissue macrophages (including microglia), is strongly reduced in mice lacking the receptor.[25-27]

Histology

Microglial cells also have elongated nuclei forming thin, highly branched projections and relatively little cytoplasm. Immunohistochemical staining is the best method of visualizing microglia.[22]

Function and Role in Immunity

Since microglial cells in the normal brain and spinal cord are not active, they are sometimes called resting microglial cells. Microglia mediate a range of brain activities in healthy settings, including synaptic pruning and remodeling. Bidirectional communication between neurons and microglia is very important for neuronal circuits and brain connections.[28,29] However, an inflammatory disorder of the CNS, they become immune effector cells, migrate to the lesion site, proliferate and become antigen-presenting cells, and encounter invading organisms together with T lymphocytes, operate as a double-edged sword, either relieving or exacerbating the injury. It also performs an active phagocytic function, and its cytoplasm is filled with lipids and cell debris.[1]

Also, in response to tissue damage from different causes, microglia transform into large cells. They are amoeboid phagocytic cells and therefore CNS representatives of the macrophage-monocyte defense system.[22] When a pathogen or brain injury is encountered, upon activation, the morphology becomes more amoebic, and during the change of morphology, cell surface receptor expression, secretion of chemokines, and cytokines also change.[7] Monocytes from adjacent blood vessels combine microglial cells.[1]

Activation

Microglial activation is divided into pro-inflammatory activation (classic, M1) or anti-inflammatory activation (alternative, M2). M1 microglia cells produce pro-inflammatory cytokines such as interleukin (IL)-1 and tumor necrosis factor (TNF) and express nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which produces superoxide and reactive oxygen species (ROS). M2 microglia cells support the release of anti-inflammatory factors, neurotrophic factors, and other growth factors as well as the healing process.[7] Microglia activation is frequently linked to neurodegeneration, a degenerative process that underpins the pathophysiology of neurodegenerative disorders.

Associating Conditions

The number of microglial cells increases in the presence of disorders such as Alzheimer's disease (AD), Parkinson's disease (PD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and AIDS, after trauma or ischemic injury. Most of these new cells are monocytes that have migrated from the blood.[1,30]

Alzheimer's disease is a progressive neurodegenerative disorder afflicting mainly the elderly and is the most common cause of dementia. There are accumulation of extracellular amyloid-beta (Aβ) peptides, derived from the cleavage of amyloid precursor protein (APP), and intracellular deposits of hyperphosphorylated tau. Astrocytes and microglia express apolipoprotein E (APOE) under the control of nuclear hormone receptors, and it plays an important role in Aβ phagocytosis by microglia.[31,32] In the brain, microglia mount an immediate immunological response to damaging stimuli such as misfolded proteins like Aβ. Microglia's physiological and beneficial functions are diverted if the response does not resolve. In the brains of AD patients and AD mice models, activated microglia, immunoglobulins, and complement components are all linked to Aβ deposition. Microglial stimulation causes morphological changes such as process shortening and soma enlargement, changes in surface

phenotype and secretory profile, and enhanced proliferative responses.[33,34]

Parkinson's disease is the second most common neurodegenerative disorder, characterized by resting tremors, bradykinesia, postural instability, cognitive impairment, and autonomic dysfunction. There is an accumulation of intracellular inclusions (Lewy bodies or Lewy neurites) and the loss of dopaminergic neurons in the substantia nigra pars compacta. Genome-wide association analysis identified the human leukocyte antigen gene, which is expressed particularly in microglia, as a genetic risk factor for late-onset PD. It is also linked to the R47H variation of the microglial triggering receptor expressed on myeloid cells-2 (TREM-2).[35,36]

Amyotrophic lateral sclerosis is characterized by degeneration of both upper and lower motor neurons in bulbar and spinal regions leading to fasciculation, weakness, atrophy associated with hyperreflexia, and spasticity. It is the most common motor neuron disorder in adults and has a fatal progression. Microglial activation with increased expression of TSPO in the brain has been found in ALS. [30]

Multiple sclerosis is characterized by multiple focal lesions, continuing demyelination, and a lack of remyelination. Microglia, peripheral macrophages, T lymphocytes, and plasma cells infiltrate active MS lesions, which are frequently present in early relapsing-remitting MS. Depending on the existence of intracytoplasmic myelin breakdown products, these lesions might be demyelinating or post-demyelinating. Microglia/macrophages containing both minor and major myelin proteins (myelin/oligodendrocyte glycoprotein, 2'3'cyclic nucleotide 3'-phosphohydrolase protein, and myelin-associated glycoprotein) are seen in early demyelinating lesions (myelin basic protein, and proteolipid protein). Only significant myelin proteins are seen in late demyelinating lesions.[37] According to the marker transmembrane protein 119 (TMEM119), which is expressed exclusively on microglia and not on macrophages, the initial pool of phagocytic cells in an early MS lesion is made up of around 40% microglia. As the lesion advances, peripheral macrophages are more recruited. The presence of purinergic receptor P2Y12 (P2RY12), an ADP-responsive G-protein coupled receptor unique for the ramified processes of microglia observed in the resting state, indicates that almost none of the microglia in an active lesion are homeostatic. There are nodules of activated microglia even in the normal-appearing white matter of MS patients, but whether these microglia are homeostatic or activated is controversial because a study indicated a decrease of P2RY12 while another showed intact P2RY12 gene expression. [38-41]

PSYCHIATRIC DISORDERS

Autism spectrum disorder (ASD) is a developmental disability defined by persistent deficits in social interaction and the existence of confined, repetitive patterns of behaviors, interests, or activities. It is believed to affect 18.5 per 1,000 children under the age of eight, and males are 4.3 times more likely than females to be affected.[42] As shown in a recent study, an exaggerated translation in microglia causes autism-like behaviors in male mice. Although microglial eukaryotic translation initiation factor 4E (eIF4E) overexpression enhances translation in both sexes, it only increases microglial density and size in males, which is accompanied by a microglial shift from homeostatic to functional, with increased phagocytic capacity but decreased motility and synaptic engulfment. The disruption of male microglia function is a major contributor to sex-biased ASD.[43]

Major depressive disorder is a common mental disorder characterized by abnormalities of various brain cell types. Microglia, the major resident immune cells, have been shown to have a crucial role in the genesis and course of depression. Microglia-derived neuroinflammation-related characteristics have been highly linked to depression in patients. Pro-inflammatory cytokines are persistently increased.[44-47]

Immune system changes, as well as neuroinflammation, contribute to progressive brain changes. Inflammatory cytokines released by activated microglia induce indoleamine 2,3-dioxygenase (IDO) activity and deplete CNS tryptophan, resulting in reduced serotonin levels and changes in glutamate, dopamine, and downstream ROS. In double-blind, randomized trials of patients with recent-onset schizophrenia, minocycline added to an antipsychotic demonstrated a significant reduction in symptoms and additive cognitive benefit when compared to antipsychotic monotherapy.[48,49] Recent research has found that microglia play a substantial role in excessive synaptic destruction in schizophrenia pathogenesis. In postmortem brain tissue from schizophrenia patients, synapse density was shown to be reduced. In patient-derived neuronal cells and isolated synaptosomes, synapse removal was higher. Physiologically and pathologically, several molecules such as CX3C chemokine ligand 1/CX3C chemokine receptor 1 (CX3CL1/CX3CR1), cluster of differentiation

47/signal-regulatory protein (CD47/SIRP), and lectins are implicated. Also linked to enhanced neuronal complement deposition and synapse uptake are schizophrenia risk-associated polymorphisms in the human complement component four locus. In this regard, the antibiotic minocycline inhibits microglia-mediated synapse uptake *in vitro* and is linked to a slight reduction in incident schizophrenia risk when compared to other antibiotics, suggesting that excessive pruning could be a target for delaying or preventing the onset of schizophrenia in high-risk individuals.[50,51]

MOLECULAR IMAGING

Microglia cells play a role in neuroinflammation caused by many underlying disorders such as stroke, trauma, AD, schizophrenia, major depression, ALS, and some methods such as MRI and PET, which are used to image these cells, have been described in the literature.[11,12,17-19,21] While diffusion-weighted imaging (DWI) as an MRI technique is used to measure cellular changes associated with neuroinflammation and microglial activation, multi-compartment DWI methods such as neurite orientation dispersion and density imaging (NODDI) can detect water diffusion from different tissue compartments, including the extra neurite compartment.[52] In the NODDI method, diffusivity in the extra-neurite compartment is measured by orientation dispersion index (ODI). The ODI was developed to quantify how changes in neurite distribution affect water diffusion in the extra-neurite space without accounting for the potential contribution of cells such as microglia to quantitative measures of ODI. Since microglia constitute 5-15% of all glial cells and glial cells in the extra-neurite compartment a large percentage of non-neuronal cells in mice (35%) and human brain (50%), they undergo significant changes in both morphology and density in response to inflammation. Therefore, Microglial activation and microglial-mediated neuroinflammation can be evaluated in the DWI sequence, as the result of these changes significantly alters the degree of diffusion restriction in the extra-neurite compartment.[23, 53-56]

The neurite orientation dispersion and density imaging is sensitive to capturing changes in microglial density, increased fullness of the extra-neurite space is associated with more restricted diffusion, and there is a significant statistical correlation between quantitative measures of ODI. Therefore, MRI is important in detecting cellular changes associated with microglial activation during neuroinflammation.[12] Therefore, monitoring microglial activation through changes in microglial density during the stages of neuroinflammation is of great importance in terms of clinical diagnosis of NODDI, treatment of neuroinflammation, patient risk classification, and clinical care and research of neuropsychiatric disorders.[57,58] For example, in a recent study, the changes in ODI or neurite density index (NDI) were investigated to predict the later emergence of interferon-alpha (IFN-α)-induced fatigue in 18 patients receiving IFN-α based treatment for hepatitis-C using NODDI. An acute increase in NDI was observed in patients administered IFN-α and predicted the development of long-term fatigue. This indicates that NODDI may be useful as a potential *in vivo* biomarker for detecting central effects of peripheral inflammation.[56]

Although TSPO has been a traditional method for evaluating microglial activation (for example for monitoring AD progression and susceptibility to anti-inflammatory treatments), it has some limitations such as high non-specific binding, low brain uptake, genotypic variation, complex tracer kinetics, plasma variability, and TSPO polymorphism which causes large differences in binding affinity between patients.[59-62]

Although upregulation of TSPO has been associated with the M1 activation status of microglia (less commonly M2 activation), a decrease in TSPO protein expression has been observed in human adult microglia and monocyte-derived macrophages in pro-inflammatory conditions.[63,64]

Therefore, in order to detect microglial activation in PET imaging, it is necessary to monitor different microglial phenotypes and to know the changes in the expression of some other receptors and enzymes during microglial activation. For example, cannabinoid type 2 (CB2) receptor, cyclooxygenase-2 (COX-2), purinergic receptor P2X7, and ROS are the recently developed PET tracers for imaging in neuroinflammation.[65,66]

PET TRACERS TARGETING

Cannabinoid Type 2 (CB2) Receptor

Cannabinoid receptors are a kind of G-protein-coupled receptors. While the CB1 receptor is expressed in the CNS, CB2 is predominantly expressed in peripheral organs as well as microglia and neurons, increasing significantly in neuroinflammatory conditions. [^{11}C] A-836339**,** [^{11}C] NE40, [^{18}F]29 (^{18}F-labeled analog of A-836339), [^{11}C]

RS-016, [^{11}C]RS-056, [^{18}F]RS-126 and [^{11}C]RS-028 are examples for radiotracers targeting the CB2 receptor. Among these [^{11}C]RS-016, [^{18}F]RS-126, and [^{11}C] RS-028 have more than 10,000-fold selectivity for CB1.[56-65,67-72] Thus, while CB2 may only be useful in the earliest stages of neurodegenerative disorders, high selectivity for CB2 rather than CB1 of radiotracers is required to eliminate a non-specific PET signal due to the abundance of CB1 in the CNS.[65]

Cyclooxygenase-2 (COX)

Cyclooxygenases play a role in the arachidonic acid cascade and activation of inflammatory pathways. Although COX-1 and COX-2 are expressed in the brain, COX-2 is rapidly overexpressed in the case of neuroinflammation.[73] COX-2 targeting tracers have some limitations including high blood pool retention, limited uptake in target organs, high amounts of non-specific binding, relatively low affinities (>50 nM), and rapid metabolism or, substantial defluorination in the case of ^{18}F-labeled compounds.[74,75] [^{11}C] MC1 and [^{18}F]1 (^{18}F-labeled analog of celecoxib) are examples for COX-2 selective radiotracers.[76,77] [^{11}C] MC1 was used in LPS-induced neuroinflammation and upregulation of COX-2 was observed [78,79] [^{18}F]1 may be a valuable COX-2 radiotracer *in vivo* due to its good *in vitro* affinity, high metabolic stability, and high brain uptake.

P2X$_7$ Receptor (P2X$_7$R)

It is expressed in multiple cell types of the myeloid cell line and mainly in microglia in the CNS. Adenosine triphosphate (ATP) is the natural agonist of this receptor, and although its affinity for the receptor is low, it is activated only at high ATP concentrations (mM). Activation of P2X$_7$R plays a key role in triggering neuroinflammation and leads to the pro-inflammatory release of cytokines like interleukin 1 beta (IL-1β). P2X$_7$R is associated with the pro-inflammatory phenotype of microglia and its functional upregulated expression in CNS disorders.[80-82] [^{3}H]A-740003, [^{18}F] EFB, [^{11}C]JNJ-54173717 have good affinity toward P2X$_7$R.[83-85] P2X$_7$R may be a promising alternative for TSPO-PET in the imaging of microglial activation.[82,84]

Reactive Oxygen Species

Nitric oxide (NO) and superoxide are formed as a result of increased inducible nitric oxide synthase (iNOS) expression and high levels of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity and activation of pro-inflammatory microglia and astrocytes in the oxidative stress state. Under normal conditions, superoxide is removed from cells by the action of superoxide dismutase (SOD). However, under high levels of NADPH oxidase activity, superoxide can react with NO to form peroxynitrite (ONOO-). Peroxynitrite can damage macromolecules in the cytoplasm and nucleus, including lipid peroxidation, DNA strand breaks, and oxidation of sulfur groups in proteins.[86,87] The development of PET radiotracers that can monitor superoxide levels in the CNS has led to the monitoring of pro-inflammatory neuroinflammation in neurodegenerative disorders and also the development of inhibitors of this enzyme for therapeutic purposes in neurodegenerative disorders also due to the key role of NADPH oxidase in oxidative stress.[75] Although [^{18}F] FDMT (^{18}F-labeled analog of fluorescent probe dihydroethidium) has been shown to be sensitive in measuring superoxide levels in cells and tissues using microscopy and optical imaging methods, it is not sufficient for imaging superoxide levels during neuroinflammation due to not crossing the blood-brain barrier (BBB).[88,89] [^{3}H] Dihydroethidium is oxidized by both superoxide and hydroxyl radicals, having high brain uptake in microPET imaging studies.[65,90] [^{18}F] ROStrace is a suitable radiotracer for PET imaging of superoxide levels in the CNS because it rapidly crosses the BBB and is retained in the brain of animals treated with lipopolysaccharide. However, [^{18}F] ox-ROStrace (the oxidized form of [^{18}F] ROStrace) does not cross the BBB.[88]

11C-labeled dihydroquinoline derivative ([^{11}C] DHQ1) is an analog of NADH/NADPH that can cross the BBB and become trapped in the brain, which can be used in imaging oxidative stress.

DISEASE-MODIFYING THERAPIES

Interferon-beta (IFN-β), glatiramer acetate, fingolimod, teriflunomide, alemtuzumab, and minocycline are agents that can be used in reducing the microglial activation. IFN-β and glatiramer acetate have an indirect effect on microglia by producing a T-helper 2 (Th2) shift in the lymphocyte profile, which reduces their pro-inflammatory phenotype. In microglia, glatiramer acetate produced an alternatively activated phenotype. Teriflunomide has been shown *in vitro* to inhibit microglial proliferation without affecting the microglial phenotype. Fingolimod can enter the CNS and binds to sphingosine 1-phosphate (S1P) receptors on microglia, causing TNF-α, IL-1β, and interleukin-6 (IL-6) to be downregulated. Alemtuzumab appears to have an indirect effect on microglia by causing reconstituting lymphocytes to produce more

brain-derived neurotrophic factors, platelet-derived growth factors, and ciliary neurotrophic factors. The antibiotic minocycline reduces the severity of sickness in an experimental autoimmune encephalomyelitis model by inhibiting microglial activation.[91-97]

In conclusion, since microglia play an important role in the normal physiology of the brain (brain development, maintenance of homeostasis) as well as in neuroinflammation and neurodegeneration, their detection is very important, especially in disease states. Multi-compartment DWI methods such as NODDI and PET imaging can be used for imaging microglial activation. Although TSPO-PET has conventionally been used in imaging of neuroinflammation, due to being highly dynamic microglia activation in neuroinflammation and protein expression is dependent on both microglial phenotypes, more specific PET radiotracers targeting (such as CB2, COX-2, $P2X_7R$, and ROS) have been developed. Although these are involved in the pro-inflammatory phenotype (M1) of microglial activation, there is also a need for radiotracers such as the P2Y12 receptor to be involved in the anti-inflammatory phenotype (M2), which is G-protein-coupled and overexpressed in anti-inflammatory phenotype.

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