Review Article

Neuroinflammation

Contemporary anti-inflammatory treatment approaches

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ABSTRACT

تحققنا من فكرة نهج علاج المضادة للالتهابات الممكنة لاضطرابات الالتهابية في الجهاز العصبي المركزي. وتم بحث المقالات المستخدمة لهذا الاستعراض من خلال ببميد Pubmed وPsycINFO والباحث العملي Google Scholar التي نشرت خلال الفترة من يناير 2000م إلى يوليو 2013م. فالجهاز العصبي المركزي لديه آلية دفاعية خاصة به. فالعلاقة المتبادلة بين الخلايا العصبية والنظام المناعي تُجرى عبر جزيئات صغيرة تسمى بالسيتوكينات التي تفرز من الخلايا الدبقية. في دراسة سابقة اقترح أن الخلل السيتوكينات يسهل تطوير اضطرابات الجهاز العصبي المركزي. على سبيل المثال، يتم رفع مستوى انترلوكين 6- في الخلية النجمية أثناء نوبات الاكتئاب، في حين تتلف محاور عصبية من قِبل الخلايا الليمفاوية والخلايا الدبقية الصغيرة تفعل في التصلب المتعدد. أثبتت العديد من الدراسات أن السيتوكينات الالتهابية والمركبات ترتبط ارتباطاً وثيقاً بالاضطرابات العصبية والنفسية والعصبية. نستعرض هنا الأدلة من تلك البحوث التي تدعم خيارات علاج مضاد الالتهابات لاضطرابات الجهاز العصبي المركزي .

We investigated the idea of possible anti-inflammatory treatment approaches for inflammatory disorders in the CNS. The articles used for this review were searched through PubMed, PsycINFO, and Google scholar and published between January 2000 and July 2013. The CNS has its own type of defensive mechanism. The crosstalk between neurons and the immune system take place via small molecules called cytokines that are secreted from glial cells. Previous study suggested that the imbalance of cytokines facilitates the development of CNS disorders. For instance, the interleukin-6 level is raised in the astrocyte cell during depressive episodes, while axons are damaged by the activated lymphocytes and microglia in multiple sclerosis. Several studies demonstrated that cytokines and inflammatory compounds are closely linked to neuropsychiatric and neurodegenerative disorders. Here, we have accumulated and summarized evidence from those papers that support the anti-inflammatory treatment options for inflammatory CNS disorders.

Neurosciences 2014; Vol. 19 (2): 87-92

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The CNS is a complex organ that is separated by the blood brain barrier (BBB) from the rest of the body. The CNS is an immunologically privileged site. It has its own defensive mechanism provided by glial cells. Glial cells secrete cytokines and chemokines in the brain and participate in antigen presentation. When a pathogen enters the body, the innate immune system immediately raises the first line of defence by employing eosinophils, basophils, phagocytic cells such as dendritic cells, and macrophages.[1] The adaptive immune system works via B cells that are involved in the humoral immune response,[2] and T cells that are involved in a cell-mediated immune response. The B and T cells constitute 85% of the total lymphocytes involved in the process. The remaining 15% of cells are the natural killer (NK) cells. The T cells are of several types: helper T cells (Th), cytotoxic, memory, regulatory (Treg), and natural killer T cells. Among them Th and Tregs are immune regulator cells that modulate cytokine production in the brain. The Th cells are again of 2 types (Th1 and Th2). The Th1 produces type-1 cytokines such as interleukin-2 (IL-2), interferon-γ (IFN-γ) and tumor necrosis factor-alpha (TNF-α), while Th2 cell produces IL-4, IL-5, and IL-10. Cytokines are small signaling molecules that

Disclosure. The authors declare no conflicting interests, support or funding from any drug company.

interact with immune cells. Cytokines are produced from the peripheral blood and astrocyte and microglia cells of the brain. The IL-1, IL-6, and TNF-α were found in increased levels in many CNS diseases such as stroke, cerebral inflammatory, and neurodegenerative diseases. These cytokines may affect apoptotic processes, and reduce synaptic activity and neurogenesis in the hippocampus.[3] A growing body of literature supports the theory that cytokines cause a neurotoxic environment in the brain.[4,5] For example glial cells produce IL-1 and TNF-α in the brain, which causes neurotoxicity. Cytokine induced neurodegenerative disorders could be mediated by many mechanisms such as i) release of nitric oxide (NO) from astrocytes, ii) N-methyl-D-aspartate (NMDA) receptors,[6] and iii) glutamate uptake by astrocytes.[7] Ma et al[8] in 2000 reported that IL-6 causes neurotoxicity mediated by excess formation of NO on hippocampal neuronal culture. A recent study reports that neurotoxicity in the brain could be mediated by p38α and p38β mitogen-activated protein kinase (MAPK).[9]

Neuroinflammation and associated disorders. Inflammation in the CNS is developed due to the activation of astrocytes and microglial cells that produce major inflammatory mediators as well as neurotoxic free radicals. Most of the CNS disorders such as stroke, multiple sclerosis (MS) and Alzheimer's disease (AD), and psychiatric disorder like depression, schizophrenia, autism, narcolepsy, anorexia nervosa, obsessive-compulsive disorder (OCD), and bipolar disorders are often associated with the modulation of the cytokine system in different brain regions. In the brain, several important pathways might be affected by the cytokines of the immune system. Thus, cytokines influence brain functions and behaviors.[10] In 2011, Capuron and Miller[11] proposed several pathways that might be influenced by cytokines. The authors mentioned the effects on the synthesis, availability, reuptake, and excitotoxicity of neurotransmitters by cytokines. They demonstrated that the availability of serotonin may be affected by cytokines in the kynurenine and MAPK pathways. Moreover, dopamine reuptake, synthesis, and glutamate excitotoxicity are also influenced by cytokines. Previous authors also demonstrated the effect of cytokines on neuroendocrine function, neural plasticity, and neural circuitry. The function of the neuroendocrine system, neural plasticity, and neural circuitry can be altered with the presence of cytokines, which may lead to the unwanted CNS disorders.[11] The BBB contains endothelial cells that produce tight junctions. Glial cells such as astrocytes, and pericytes serve the BBB to maintain its structure and functional activities. An intact BBB is important to maintain the hemostasis of the brain. However, inflammatory cytokines, and reactive oxygen species (ROS) could damage the BBB. Disruption of the BBB leads to neuroinflammation, neurodegeneration, and neuronal dysfunction.[12,13] Disruption of the BBB causes various diseases such as MS,[14] and autism.[15] At present, a large number of studies investigate the role of the IDO (indoleamin-2-3-dioxygenase) enzyme in various CNS related disorders. This enzyme is primarily found in astrocyte cells. The IDO enzyme can be activated by a pro-inflammatory cytokine, such as IFN-γ. The IDO enzyme is the first rate-limiting tryptophan degrading enzyme in the kynurenine pathway and its activation reduces the availability of serotonin (5-HT).[16,17] Activation of the IDO enzyme causes unwanted neurotransmission, and production of neurotoxic metabolites such as 3-hydroxykynurenine (3-HK) and quinolinic acid (QUIN). These toxic metabolites (3-HK, QUIN) damage neurons.[18] Nevertheless, the activity of IDO can be inhibited by anti-inflammatory cytokines, such as IL-4, and IL-10.

Purpose of the review. The purpose of this review paper was to analyze CNS disorders from an inflammatory perspective. A growing number of studies have reported the association of CNS related disorders with inflammation. It is established that the brain has its own immune system, which is separated from the rest of the body by the BBB. However, this privileged site (brain) of the body and its immune function could be weakened in many situations such as a leaky BBB. We summarize the contemporary evidence from those articles that explain brain diseases from an inflammatory perspective. We have also accumulated and reviewed articles that provide information on the anti-inflammatory treatment options for inflammatory CNS disorders. In this review, we summarize the underlying mechanism of neuroinflammation and possible treatment strategies in **Table 1**.

Depression. Cytokines interact with many areas of the brain that are known to be involved in depression. Interferon-α induces depressive episodes by increasing IL-1, IL-6, IFN-γ, TNF-α, haptoglobin, and neopterin levels in the CSF.[19] Cytokines may cause depression by 3 possible mechanisms: hypothalamo-pituitary-adrenocortical (HPA) axis activation, neuronal serotonin transporter activation, and IDO enzyme stimulation. Previous studies reported that there is a correlation between cytokines and HPA axis.[20,21] They demonstrated that hyperactivity of the HPA axis is associated with the increased amount of IL-1 and IL-6 in major depression. The idea of cytokine induced

serotonin deficiency during depression was reported earlier by Zhu et al in 2006.[22] The authors reported that IL-1β and TNF-α intensely control neuronal serotonin transporter activation. The IDO enzyme is induced by the pro-inflammatory cytokines including IL-1, IFN-γ, IFN-α, and TNF-α, which leads to a peripheral tryptophan deficiency.

Treatment. Anti-inflammatory therapy could have beneficial effects in major depression.[23] In the case of depressive symptoms, the combination of reboxetine and celecoxib for 6 weeks was reported to be more effective than reboxetine alone. Moreover, celecoxib is another option, which was found to be an effective treatment option for depressive and manic episodes in bipolar disorder.[24]

Schizophrenia. A large number of studies have shown that infection during pregnancy is associated with the child developing schizophrenia in adult offspring. In addition, CNS infection increases the risk for later schizophrenia. A low level of IL-2 and IFN-γ cytokines in the CNS, increased level of IL-6 in plasma, and IL-4 in the CSF are reported in schizophrenia. These cytokines cause an imbalance in the tryptophan/kynurenine pathway between IDO and tryptophan-2,3-dioxygenase. It has been demonstrated that an imbalance in the tryptophan/kynurenine metabolism leads to an elevated production of kynurenic acid (KYNA) in the brain that again causes an imbalance in glutamatergic neurotransmission, resulting in an NMDA antagonism in schizophrenia.[25] An elevated level of KYNA has also been found in the prefrontal cortex of schizophrenic patients.[13,26]

Treatment. Evidence suggests that cyclo-oxygenase-2 (COX-2) inhibitors reduce KYNA levels.[23] A celecoxib and risperidone combination was found to be more effective than risperidone alone in a double blind study.[27] In 2013, Muller and his colleagues[28] in their review paper claimed that inflammation might be a major factor in the progression of the pathophysiology of schizophrenia. They further describe that cytokines control the activation of IDO enzymes. The IDO enzyme converts tryptophan to kynurenine metabolites such as KYNA. An increased level of KYNA in critical areas of the brain causes lowered glutamatergic neurotransmission. In this case, the production of prostaglandin E2 and the expression of COX-2 can be enhanced. The authors proposed that COX-2 inhibitors might positively contribute to reducing inflammation in the early stages of schizophrenia.

Autism. Accumulating evidence suggests an association between autism spectrum disorders (ASD) and inflammation in the brain.[29-31] Moreover, increased cytokine levels during the early stage of life might have a role in ASD development. In addition, increased levels of pro-inflammatory cytokines such as IL-1α, IL-1β, IL-6, and TNF-α were found in brains associated with hippocampal and cerebral damage in ASD.[32] Furthermore, disruption of the BBB and a leaky BBB

Table 1 - Mechanism of neuroinflammation of inflammatory disorders of the CNS, and possible treatment strategies.

Disease	Underlying inflammation	Treatment
Depression	Pro-inflammatory cytokines influence IDO enzymes in kynurenine pathway [20,21,22]	Reboxetine and celecoxib[24]
Schizophrenia	Pro-inflammatory cytokines cause imbalance in tryptophan/kynurenine pathway Glutamatergic neurotransmission[25,26]	Celecoxib and risperidone combination[27]
Autism	Increased cytokines causes damage in hippocampal and cerebral cortex[32] Disruption and leaky BBB by IL-6[33,34]	Natural flavonoid luteolin[36]
Obsessive-compulsive disorder	TNF-α polymorphisms[37]	Celecoxib in combination with fluoxetine[38,39]
Multiple sclerosis	Axonal damage due to inflammation[40]	Natalizumab, CCR-1 agonist[42]
Parkinson's disease	Increased pro-inflammatory cytokines in substantia nigra, striatum, and CSF[44] Activation of NF-κB	NSAIDs inhibit COX enzyme[45,46]
Alzheimer's disease	Aβ42 induces increased cytokine production Pro-inflammatory cytokines are involved in the neurotoxic cascade[47]	COX-1 inhibition has been reported to reduce neuroinflammation[50]

IDO - indoleamin-2-3-dioxygenase, BBB - blood brain barrier, IL - interleukin, TNF - tumor necrosis factor, CCR - chemokine receptor, NSAID - non-steroidal anti-inflammatory drugs, COX - cyclo-oxygenase, NK - natural killer

by IL-6 and TNF-α have also been reported in the fetal brain.[33,34]

Treatment. The natural flavonoid luteolin could be useful because it inhibits human mast cell TNF release. Flavonoid-related epigallocatechin gallate is an mammalian target of rapamycin inhibitor that may produce beneficial effects in brain inflammation and autoimmune T cell activation.[35,36]

Obsessive-compulsive disorder. Obsessive-compulsive disorder is linked to autoimmune disorders, and reported with TNF-α polymorphisms.[37] Acute or chronic infection, inflammatory process, or a post-infectious immune response may be involved in the pathogenesis of OCD.

Treatment. Celecoxib in combination with fluoxetine has been reported to diminish the symptoms of OCD more effectively than fluoxetine plus placebo.[38] The COX-2 inhibitor (celecoxib) reduces the production of pro-inflammatory cytokines, inhibits the synthesis of PGE2 (one kind of prostaglandin),[39] and also prevents kainic acid induced neuronal death.

Multiple sclerosis. The activated microglia, T- and B-lymphocytes cause the autoimmune disorder MS. Multiple sclerosis is characterized by demyelination in which axonal damage becomes high in the presence of inflammation, macrophages, and CD8+ T cells.[40] In MS, damage of the BBB causes edema, which in turn enhances extracellular pressure and may thus injure axons.[41]

Treatment. Natalizumab (a monoclonal antibody) works against the adhesion of α-4 integrin in MS. Moreover, a chemokine receptor (CCR-1) agonist can be used for immune cell traffic across the BBB.[42] Both IFN-β and phosphodiesterase IV inhibitors can also be used to reduce the level of pro-inflammatory cytokines in the CNS.

Parkinson's disease. Neuroinflammation and microglial activation are involved in the pathogenesis of Parkinson's disease (PD).[43] Toxin induced PD has been reported to show an increased level of IL-1β, IL-6, and TNF-α in the basal ganglia and CSF. Increased levels of IL-1β, and IL-6 in the CSF and TNF-α in the striatum and CSF have been found in many studies. Moreover, activated T-lymphocytes and increased expression of pro-inflammatory cytokines are reported in the substantia nigra.[44] In a 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine induced model of PD, the activation of the nuclear transcription factor NF-κB has been reported, which causes the synthesis of COX-2 enzyme.

Treatment. Non-steroidal anti-inflammatory drugs (NSAIDs) may exert their neuroprotective actions not only by inhibiting COX enzymes but also by acting on NF-κB, inducible nitric oxide synthase, and peroxisome proliferator activated receptor gamma suppressing the formation of dopamine quinones, scavenging ROS, and reactive nitrogen species activity, and probably by other unknown mechanisms.[45,46]

Alzheimer's disease. In cases of AD, accumulation of amyloid plaques consisting mainly of Aβ42 triggers neuroinflammatory processes that lead to a modified production of cytokines based on microglia and astrocyte cell activation.[3] Alzheimer's disease is also associated with increased plasma levels of TNF-α,[47] and IL-1 that are involved in the neurotoxic cascade.

Treatment. Experimental immunological therapies include the application of immunoglobulins, and active immunization against Aβ42 may be suggested.[48,49] A recent study in an animal model suggests that COX-1 inhibition reduces neuroinflammation, neuropathology, and improves cognitive function.[50] The NSAIDs have not been reported to reduce the risk of AD, but the effectiveness of NSAIDs is still being investigated in the research laboratories. New NSAID treatment options will be available in the near future.

Bacterial and viral infection of the CNS. It has been reported that bacteria and viruses contribute to the progression of disease in the brain. *Orientia tsutsugamushi* is an intracellular microorganism that enters the CNS through circulating monocytes and causes meningitis.[51] *Ehrlichia chaffeensis* also causes inflammation in the brain, which leads to meningoencephalitis. *Chlamydia pneumonia* is another intracellular bacterium, which can enter the CNS and produce neuroinflammation. Boelen et al,[52] stated that *Chlamydia pneumonia* has a crucial impact on the progression of AD. An extracellular pathogen such as *Borrelia burgdorferi* could infect circulating monocytes and enter the CNS through the BBB. *Borrelia burgdorferi* may also produce AD, and *Helicobacter pylori* could also be responsible for idiopathic PD.[53]

A growing number of studies report that many viruses have a potential role in infection in the CNS. Meningitis or encephalitis could be mostly mediated by a virus. Henipaviruses (Hendra and Nipah) may enter the CNS from the bloodstream and cause encephalitis/meningitis through neural infection.[54] Enterovirus 71, West Nile virus, and Chikungunya virus also cause encephalitis/meningitis. Children who are infected by influenza virus may manifest encephalitis/encephalopathy.[55] A previous study[56] reported a link between AD and herpes simplex virus 1. Moreover, human immunodeficiency viruses (HIV) enter the CNS and bind with the astrocytes. This binding interaction induces a neuroinflammatory response such as rapid

production of cytokine in the CNS.[57] It is estimated that 50% of HIV patients develop cognitive impairment.[58] A neuroinflammatory mechanism associated cognitive dysfunction is reported in HIV patients.[59]

In summary, we discussed the involvement of neuroinflammation in neuropsychiatric and neurodegenerative disorders, and its treatment. Neuroinflammation associated with psychiatric and neurodegenerative disorders becomes a major threat when the pro-inflammatory cytokines are not within the normal range. Accumulating evidence suggests increased levels of pro-inflammatory cytokines in both neuropsychiatric and neurodegenerative disorders. Such increments should be controlled within the normal range. On one hand, most of the previous studies recommended that the combination of NSAID and antipsychotics might contribute positively in neuropsychiatric disorders. On the other hand, immunosuppression through the reduction of a pro-inflammatory component in the glial cells could have beneficial activity in the cytokines as well as inflammation induced neurodegeneration. Neuroinflammation is a multicomponent phenomenon. Therefore, a cocktail of therapeutic agents including anti-inflammatory drugs and early immunization might be a well-judged option in balancing the inflammatory components. We suggest anti-inflammatory drugs as palliative treatment option for CNS disorders. To some extent, antipsychotic drugs cause liver injury in patients with high body weight, and poor liver function; therefore, antipsychotics are not a well-judged option.

Acknowledgments. *We would like to acknowledge Dr. Md. Mahbubur Rahman, and Muhammad Shohel for their contribution. We would like to give them special thanks for providing research articles while preparing this review paper.*

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