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Neuroinflammation and Neuropathology

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This review addresses the current understanding of the role of autoimmune neuroinflammation in the pathogenesis of vascular, neurodegenerative, and other diseases of the nervous system. The mechanisms of responses of resident CNS cells (glial cells, astrocytes) and peripheral immune system cells are presented. The therapeutic potentials of phosphodiesterase inhibitors, which have antiaggregant properties and can suppress autoimmune inflammation, are discussed. The phosphodiesterase inhibitor dipyridamole is regarded as a potential drug for this purpose.

Keywords: neuroinflammation, microglia, astrocytes, blood–brain barrier, dipyridamole.

Most practicing physicians currently regard cerebrovascular disease as a state or process due exclusively to impairments to cerebral perfusion inducing an ischemic cascade of metabolic abnormalities ending with more or less severe damage to brain tissue. Neurodegenerative diseases are assessed from the point of view of the accumulation of toxic substances and impairment of the circulation of blood in the brain (microinfarcts), while the consequences of CNS trauma are seen as a more or less static state which in some cases progresses as a result of concomitant vascular disease.

Neuroinflammation is currently regarded as a major factor in the pathogenesis of many CNS diseases, this being a universal response to tissue damage. Compiling existing definitions, neuroinflammation can be defined as a process in which the intrinsic immune system of the brain is activated as a result of ischemia, trauma, infection, toxins, the neurodegenerative process, stress, or aging. This inflammation is mediated by the secretion of cytokines, chemokines, reactive oxygen species, and second messengers produced by the glia of the CNS (microglial cells and astrocytes) and endothelial and peripheral immune cells. The intensity of neuroinflammation depends on the concrete situation and the features and duration of action of the initiating stimulus or damage [1]. Neuroinflammation is a characteristic feature of virtually every neurological/neurodegenerative disease, the common thread connecting traumatic, neurodegenerative, and mental disorders [2].

The term "neuroinflammation" was initially perceived as something negative and maladapted, as most investigations focused on the pathological aspects of neuroinflammation. However, some stages in neuroinflammation are positive [3]. In many cases, including CNS damage, there is a balance between inflammatory and internal regulatory processes which help to restore functions. Like many neuropathological processes, neuroinflammation provides an example of the principle of duality, with an excitatory state and inhibition of cell activity. Depending on the situation, the same cells can show both proinflammatory and anti-inflammatory activity (see Table 1). The mechanisms of these different types of responding remain far from understood, though they remain under intense study [1].

Cerebral small vessel disease (CSVD) is at the focus of detailed study as one of the main causes of vascular dementia in the elderly. CSVD is a vascular brain disease characterized by features including recurrent strokes with persistent impairment to the blood–rain barrier (BBB) and a chronic inflammatory reaction [23]. The increase in BBB permeability allows potentially toxic and immunogenic substances to enter the brain freely [24]. Furthermore, brain cell antigens are detected in the peripheral blood of patients with lacunar strokes, while patients with leukoaraiosis have T cells sensitized to brain antigens.

Endothelial dysfunction and increased BBB permeability may promote the development of microhemorrhag-

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TABLE 1. Positive and Negative Aspects of Inflammation in Ischemic Stroke

Cell type	Negative effects	Positive effects
Microglia/macrophages [4–9]	Secretion of proinflammatory cytokines (including TNF-α and IL-1), reactive oxygen and nitrogen species, and proteases (such as MMP). Phagocytosis of viable and functioning neurons by microglia/macrophages, inducing cerebral atrophy	Decreased intensity of inflammation (release of IL-10 and TGF-β, synthesis of arginase and phagocytic activity). Late recovery processes are maintained by production of growth factors (insulin-like growth factor 1, neuronal neurotrophic factor and glial cell neurotrophic factor, facilitation of neurogenesis and plasticity, removal of necrotic material
Astrocytes [10–14]	Secretion of inflammation mediators (for example, TNF-α, interleukin-1, and MMP). Formation of edema, suppression of axon regeneration, and impairment of the BBB, formation of glial scars, and glutamate release	Uptake of extracellular glutamate, synthesis and release of neurotrophic factors. Formation of glial scars, recovery of the BBB, and neurovascular remodeling
Neutrophils [15–17]	Obstruction of microvessels, formation of reactive oxygen species, and synthesis of MMP, which promote damage to the BBB and aggravate inflammation. Stimulation of lipid peroxidation, release of proteolytic enzymes, damage to endothelial cell membranes. Increases in BBB permeability, poststroke edema, and the no-reperfusion phenomenon	N2 phenotype: ability to decrease inflammation
Dendritic cells [18]	Increases activity of MHC II and costimulated molecules which elicit lymphocyte activation	Not studied
T-lymphocytes [19–22]	Facilitate platelet and leukocyte adhesion to vascular endothelium, leading to thrombus formation and activation of inflammatory processes	Interaction of T cells with platelets can have hemostatic actions preventing hemorrhagic transformation after severe ischemic stroke

IL – interleukin; MHC II – class II histocompatibility complex proteins; TGF-β – transforming growth factor β; TNF-α – tumor necrosis factor α.

es and enlargement of perivascular spaces. Enlargement of perivascular spaces is itself a marker for BBB dysfunction and neuroinflammation [25, 26], which has been confirmed by high levels of neopterin and low levels of von Willebrand factors in plasma (both are regarded as markers of endothelial dysfunction). Neopterin is a product of activated macrophages/monocytes and reflects the level of oxidative stress [27] and von Willebrand factor is a marker of damage to endothelial cells and also a regulator of BBB permeability [28].

Two important markers for endothelial dysfunction – E-selectin and vascular endothelial growth factor (VEGF) – are associated exclusively with microhemorrhages. Soluble E-selectin is released from damaged endothelial cells and is regarded as one of the most specific markers of endothelial damage [29]. The result of increased BBB permeability is that erythrocytes may penetrate into the parenchyma, i.e., microhemorrhages [30]. This is further supported by the association between microhemorrhages and the VEGF concentration induced by leakage of blood from vessels in Alzheimer's disease [31] and stroke [32].

β-Amyloid plaques in the cerebral cortex in Alzheimer's disease activate the microglia and induce immune responses and cytokine overproduction [33], corresponding to damage to the cerebral parenchyma and vessels due to autoimmune inflammation [34].

Pathological τ protein aggregates and activation of cerebral immune system cells (astrocytes and microglia) are characteristic features of tauopathy [35, 36]. Neuroinflammation accompanying different τ protein pathologies was initially described in Alzheimer's disease by Maccioni et al. [37]. Recent studies have observed a number of mechanisms whereby hyperactivation of glial cells induces pathological neuroinflammation, which in turn influences the pathology of τ protein and accelerates neurodegenerative processes. Chronically activated glial cells induce enzymes phosphorylating τ protein, from which neurofibrillary tangles are formed, with subsequent neuron death [35–38]. In addition, glial cells can promote the spread of pathology [39]. When neurons die, the hyperphosphorylated τ protein within them activates the inflammatory cycle via a positive feedback mechanism (a vicious circle) [40, 41].

Parkinson's disease is associated with an increase in the permeability of the BBB. This leads to penetration of antigens into the midbrain, activation of microglia, and death of dopaminergic neurons [42]. The systemic inflammatory response in Parkinson's disease is apparent as activation of peripheral lymphocytes and increased serum cytokine levels, including IL-2, IL-6, and TNF-α [42].

Normal aging is linked with increases not only in the number of symptomatic and asymptomatic strokes, but also in the level of expression of systemic inflammatory factors [43] such as proinflammatory cytokines [44–46]. In the brain, this age-associated inflammation is apparent initially as chronic activation of perivascular and parenchymatous macrophages/microglia expressing proinflammatory cytokines, accompanied by increased numbers of astrocytes [47]. Chronic activation of proinflammatory markers in aging may promote increased vulnerability to neuropsychiatric disorders [48].

Chinese researchers who compared CSVD and multiple sclerosis (MS) found some interesting correlations [23].

They identified many similar features in the two processes: 1) clinical features (chronic course, exacerbated disability, impaired cognitive functions and gait, neuropsychological disorders, and sleep disorders; 2) the MRI picture(T2/FLAIR, focal and diffuse hyperintensity in the white matter, transient or constant T1 hypointensity, accumulation of contrast in foci in the acute stage and the absence of accumulation in the late stage, dilation of perivascular spaces in the centrum semiovale, a decrease in the quantity of gray matter, and dilation of the cerebral ventricles); 3) pathological gait (loss of myelin-associated glycoprotein and proteolipid protein in CSVD and selective loss of phospholipids in MS, axon degeneration, increased BBB permeability and fibrin leakage, perivascular collagenosis and inflammation, activation of the microglia and astrocytes, and lymphocyte infiltration of the perivascular spaces). The inflammatory mechanisms of both diseases have more similarities than differences, and the key clinical aspect is the availability of 13 FDA-approved disease-modifying drugs for MS while research on immunomodulation in CSVD is only just developing.

Dipyridamole was introduced into clinical practice in 1959 as a coronary lytic and antiaggregant [49]. Dipyridamole is a member of the phosphodiesterase (PDE) inhibitor family, which have not only antiplatelet, but also anti-inflammatory and immunomodulatory effects. Comparison of dipyridamole with aspirin showed that dipyridamole but not aspirin decreases nuclear factor kappa (an initiator of inflammation) activity and blocks the synthesis of monocyte chemoattractant protein (MCP-1) at the transcriptional level. Dipyridamole delays the peak in interleukin-8 synthesis and suppresses the expression of matrix metalloprotease-9 (MMP-9) in monocytes. Dipyridamole does not block the transcription or distribution of MMP-9 mRNA into polysomes, indicating that they regulate MMP-9 protein at the postinitiation stage of translation. These results demonstrate that dipyridamole has anti-inflammatory properties which may widen its efficacy in the secondary prophylaxis of stroke [50].

PDE inhibitors increase levels of the second messengers cyclic adenosine monophosphate (cAMP)and cyclic guanosine monophosphate (cGMP) in many body tissues, providing the ability to suppress inflammatory and autoimmune processes, inducing or promoting the occurrence of many diseases and states. In the last two decades, selective PDE inhibitors have demonstrated potential in the treatment of inflammation of the lungs and intestine, prostate adenoma, systemic atherosclerosis, psoriasis, and psoriatic arthropathy. In addition, PDE inhibitors have been studied for the treatment of other inflammatory states such as rheumatoid arthritis, systemic lupus erythematosus, atopic dermatitis, MS, and Alzheimer's disease. Study results suggest additional methods for the treatment of patients with inflammatory and autoimmune diseases. Leading specialists in research into CSVD take the view that the prevention and treatment of CSVD should improve the state of the BBB, the cerebral vascular endothelium, and microvascular function, and there are currently several registered drugs which have properties of nitric oxide donors and PDE inhibitors [51]. A total of 11 PDE isoforms have now been identified; dipyridamole inhibits PDE-5, -6, -7, -8, -10, and -11, having multimodal actions on different organs and tissues [52, 53].

Studies of dipyridamole using human microglial cell cultures and in the brains of mice with a model of MS and acute encephalomyelitis have shown that dipyridamole weakens increases in the levels of certain cytokines and chemokines from human microglia, while stimulation of Toll-like receptors normalizes the characteristics of activated microglia in cell cultures. In mice, dipyridamole decreased the clinical severity of acute experimental encephalomyelitis and decreased the activity of microglia and other cytological indicators of acute encephalomyelitis. This led to the conclusion that dipyridamole is an inhibitor of microglial activation and may play a positive role in MS and other neurological diseases, suppressing excess microglial activity [54].

Increasing cAMP and cGMP levels in platelets, dipyridamole reversibly inhibits their aggregation and can enhance the protective effects of endothelial nitric oxide (NO), which increases cGMP, stimulating soluble guanyl cyclase. Endothelial NO is an important regulator of vascular tone, blood flow, and tissue perfusion. Experimental NO deficit induces increases in systemic blood pressure and increases in the dimensions of myocardial and cerebral infarcts in ischemia. Other NO/cGMP-dependent effects which can be enhanced by dipyridamole include suppression of vascular smooth muscle proliferation and endothelium-lymphocyte interactions. Dipyridamole increases adenosine and prostacyclin concentrations, which decreases vascular tone and suppresses inflammation, and has antioxidant properties, which can stabilize platelets and vascular membranes and overcome low density lipoprotein oxidation [55, 56].

Increasing data provide evidence that apart from antiaggregant properties, dipyridamole may also have pleiotropic actions on nervous tissue cells and vessels. Experiments on the protection of endothelial cells in the human brain in inflammatory and metabolic impairments showed that dipyridamole significantly decreases levels of inflammatory markers and cell death after stroke and can protect the cerebral endothelium from damage in inflammation and/or metabolic impairments [57]. Studies have demonstrated the anti-inflammatory, antioxidant, and antiproliferative actions of dipyridamole. These pleiotropic effects of dipyridamole can promote improvements in treatment results when used with aspirin to prevent recurrent stroke. Treatment with low-dose dipyridamole demonstrated efficacy in preventing experimental vascular endothelial and renal impairments induced by diabetes mellitus, due to enhancement of endothelial NO signaling and decreases in renovascular oxidative stress [58, 59].

Adenosine is a powerful immunoregulatory nucleoside produced during inflammatory states to limit tissue damage. HIV infection is associated with persistent elevation of the

levels of systemic inflammation and immune activation, which have been suggested to be responsible for the increased risk of chronic non-HIV diseases. Patients receiving antiretrovirus therapy were randomized at a ratio of 1:1 to 12 weeks of taking dipyridamole (100 mg four times daily) or placebo. Dipyridamole significantly increased the extracellular adenosine level and significantly reduced T-cell activation among patients with HIV-1 infection. Dipyridamole, inhibiting cellular adenosine uptake and increasing the extracellular adenosine concentration, can suppress chronic inflammation associated with human immunodeficiency virus type 1 [60].

Infection due to coronavirus-2 (SARS-CoV-2) can induce acute respiratory syndrome, respiratory distress syndrome, hypercoagulation, hypertension, and multiorgan failure. Analysis by Chinese authors of a randomly selected cohort of 124 COVID-19 patients showed that hypercoagulation, as indicated by an elevated D-dimer concentration, was associated with disease severity. The authors' studies of FDA-approved drugs led to selection of dipyridamole, which suppressed SARS-CoV-2 replication in vitro. In experimental studies involving 31 COVID-19 patients, dipyridamole was associated with significant reductions in the D-dimer concentration ($p < 0.05$), increased blood lymphocyte and platelet recovery, and significant improvements in clinical measures in patients as compared with the control group. In particular, all eight severely ill patients receiving dipyridamole showed marked improvements: seven (87.5%) achieved clinical recovery and were discharged from hospital, while the other patient (12.5%) achieved clinical remission [61]. These data have been confirmed by other investigators, confirming the potential efficacy of dipyridamole in COVID-19 [62].

In the context of this theme, we would like to recall that the immunomodulatory properties of dipyridamole have been studied for quite some time, which is reflected in the registered indications of the drug: "dipyridamole is an interferon inducer and has a modulatory action on the functional activity of the interferon system; it increases nonspecific antiviral resistance to viral infections; is it recommended for the prophylaxis and treatment of influenza and acute respiratory tract infections" [63]. This immunomodulation is important for preventing autoimmune inflammation in cerebrovascular diseases and other central nervous system pathologies.

Completing this brief review of neuroinflammation as a participant in any severe pathological process in the nervous system, we would like to focus attention on the fact that the arsenal of neurologists and experts in other specialties has for some time included dipyridamole – a drug with pleiotropic actions on the circulation and neuroinflammation, producing not only improvements in tissue perfusion, but also modulating the autoimmune process, which is by no means a secondary component of neuropathology.

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