

# Neuronal Damage in Brain Inflammation

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**I**n contrast to traditional textbook paradigms, recent studies indicate neuronal damage in classic neuroinflammatory diseases of the brain, such as multiple sclerosis or meningitis. In these cases, immune cells invade the central nervous system compartments, accompanied by a massive breakdown of the blood-brain barrier and typical changes of the cerebrospinal fluid. On the other hand, inflammation within the central nervous system is a common phenomenon even in classic noninflammatory brain diseases that are characterized by degeneration or trauma of neuronal structures, such as Alzheimer disease, Parkinson disease, or stroke. In these cases, inflammation is a frequent occurrence but displays different, more subtle, patterns compared with, for example, multiple sclerosis. Concepts for directly protecting neurons and axons in neuroinflammatory diseases may improve the outcome of the patients. In parallel, epidemiological and animal experimental evidences, as well as first clinical trials indicate the benefit of immunomodulatory therapies for classic noninflammatory brain diseases. We review the evidence for inflammatory neuronal damage and its clinical impact in the context of these diseases.

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## INFLAMMATION IN THE BRAIN—NOT EXOTIC AT ALL

In principle, inflammation is the first response of the immune system to danger signals evoked by infection or irritation. The ability to distinguish between self and non-self enables the immune system to identify and defeat invading infectious agents. The same mechanism is responsible for the rejection of allogeneic transplants, because the immune system is able to recognize distinctive molecules that allow the identification of cells belonging to its own organism. However, this is not true for the central nervous system (CNS), where allogeneic transplants fare better than at other sites of the body, such as the skin. Moreover, the virtual absence of major histocompatibility complex class II molecules in noninflamed CNS and other specific mecha-

nisms inhibiting local immune responses led to the perception of the brain as a site with relative “immune privilege.”

Immune response is, however, possible and particular in the CNS. Acute neuroinflammation typically occurs in infectious meningitis and meningoencephalitis, where brain invasion by pathogens like viruses or bacteria triggers the breakdown of the blood-brain barrier and the subsequent influx of blood-borne immune cells into the CNS. A similar pattern is observed in the course of chronic autoimmune disorders of the brain, such as multiple sclerosis (MS). In this case, the immune system is believed to target myelin-related CNS structures and to maintain continuous brain inflammation. Thus, in these classic neuroinflammatory conditions, a specific immunological “danger signal,” be it infectious or autoimmune, elicits an immune response within the CNS.

Besides these obvious scenarios in which inflammation is accepted as an integral part of neuropathological features, inflamma-

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tory changes have been recently identified as a crucial player in primarily noninflammatory CNS disorders as well. In disorders such as Alzheimer disease (AD), Parkinson disease (PD), and Huntington disease (HD), or in X-linked adrenoleukodystrophy, the primary insult is due to degenerative or metabolic processes, whereas a crude breakdown of the blood-brain barrier with massive invasion of activated immune cells is lacking. In contrast, these disorders display signs of immunological activation, which had been classified as unspecific “reactive gliosis” in the past and were not integrated into disease concepts. However, recent epidemiological, experimental, and therapeutic studies have revealed that these rather subtle immunological alterations deserve serious attention in primary neurodegenerative disorders; apparently, immune mechanisms crucially control and promote CNS degeneration in nonneuroinflammatory diseases, like AD and stroke. Conversely, profound axonal damage and neuronal cell death have been identified in MS and infectious meningitis. These surprising findings, which are not yet fully understood, bring classic primary neuroinflammatory and neurodegenerative diseases even closer than expected. We review recent insights into the underlying molecular processes in these neurological disorders and discuss their relevance for future therapy approaches.

## NEURONAL DAMAGE IN CLASSIC NEUROINFLAMMATION

### MS—More Than a Demyelinating Disease

In patients with MS, we find early axonal pathological features, correlating with the number of infiltrating immune cells, and “black holes” and focal cortical thinning seen on magnetic resonance imaging, indicating complete tissue loss and death of neuronal cell bodies.<sup>1,2</sup> Even at early stages of disease, cognitive impairment is frequent and has been recently linked to magnetic resonance imaging signs of neuronal dysfunction. Consistently, 20% to 60% of patients with MS display electroencephalographic abnormalities, and patients with MS show

generally an up to 10-fold higher frequency of epileptic seizures compared with the general population. However, considering the evidence for MS as an autoimmune disease directed against the myelin sheath, how does neuronal damage occur?

### The Different TRAILs to Neurodegeneration in MS

In patients with MS, investigation of normal-appearing white matter reveals extensive axonal pathological features, indicating early damage of neuronal structures. Neuronal dysfunction or destruction and the increase in atrophy and the accumulation of axonal loss correlate with disability,<sup>3,4</sup> which explains the clinical observation of long-term progression similar to that in neurodegenerative diseases. Axonal damage can occur secondary to inflammatory demyelination, because the oligodendrocyte provides trophic support important for axonal function and survival.<sup>5,6</sup> Such a mechanism may also explain the presence of neurons undergoing apoptosis in the cortex of patients with MS. Moreover, activated microglial cells are found in close vicinity to neuronal perikarya and proximal dendrites in those with MS, suggesting a direct attack of destructive microglia on neurons.<sup>1</sup> But how are these microglial cells activated in the cortex (ie, from a considerable distance to the typical white matter lesions)? Subpial demyelination suggests the presence of a soluble-activating factor, presumably diffusing from the surrounding cerebrospinal fluid (CSF).<sup>7</sup> Cholesterol oxides recently have been identified as possible candidates: within the white matter plaques, the invasion of activated immune cells results in an oxidative attack on myelin lipids that decompose into cholesterol oxides, such as 7-ketocholesterol. The latter was found to accumulate in the CSF and CNS tissue of patients with MS,<sup>8</sup> and significantly correlated with clinical disability and the extent of neuronal cell death in the MS animal model, experimental autoimmune encephalomyelitis (EAE).<sup>9</sup> While 7-ketocholesterol lacks any direct detrimental effects on neurons, it promotes migration and neurotox-

icity of activated microglial cells and macrophages by triggering the expression of the inducible nitric oxide synthetase. The free radical nitric oxide, present in elevated concentrations in MS lesions, directly causes a reversible axonal conduction block—which may occur during a relapse and remission episode in MS—and irreversible degenerative injury, especially to electrically active axons<sup>10</sup> (**Figure 1**). Thus, cholesterol oxides might drive inflammation escalation that finally results in neuronal damage.<sup>8</sup> Regulatory pathways are suggested to exist in parallel and be responsible for remission phases. In our studies, we found that the endocannabinoid system is highly activated during CNS inflammation and mediates an intracellular negative feedback loop in microglial cells that leads to suppression of inducible nitric oxide synthetase induction. Thus, endocannabinoids prevent dangerous overactivation of microglial cells and, therefore, protect neurons from inflammatory damage.<sup>11</sup>

An urgent question to be answered in the past few years has been whether lymphocytes can actually directly attack neurons and axons. We and others have shown that activated CD4<sup>+</sup> T lymphocytes possess marked migratory capacities within the CNS and in fact directly interact with the soma and processes of neurons, partially leading to cell death.<sup>12</sup> But how could T lymphocytes induce neuronal apoptosis? Besides the excitotoxic glutamate pathway, a critical role has been proposed for the death ligand, tumor necrosis factor-related apoptosis-inducing ligand (TRAIL): death-mediating TRAIL receptors are found on potential target brain cells, such as neurons and oligodendrocytes; soluble TRAIL mediates neuronal cell death in human brain slices<sup>13</sup>; and TRAIL expressed by CD4<sup>+</sup> T lymphocytes induces collateral death of neurons and promotes EAE<sup>14</sup> (Figure 1). In the future, we will have to clarify the contribution of different subtypes of lymphocytes to the damage processes. In a previous report,<sup>15</sup> there was a predominance of either the CD4<sup>+</sup> or the CD8<sup>+</sup> subtype of T lymphocytes described in the lesions of patients with MS. Indeed, cultured neurons exposed to proinflammatory

cytokines express major histocompatibility complex class I molecules, so that CD8<sup>+</sup> T-lymphocyte-mediated neuronal damage could be possible<sup>16</sup> (Figure 1). However, a recent study<sup>17</sup> investigating EAE in knockout mice lacking mature CD8<sup>+</sup> T lymphocytes showed an even aggravated disease course with increased axonal damage, suggesting the important anti-inflammatory functions of this T-lymphocyte subset in vivo.

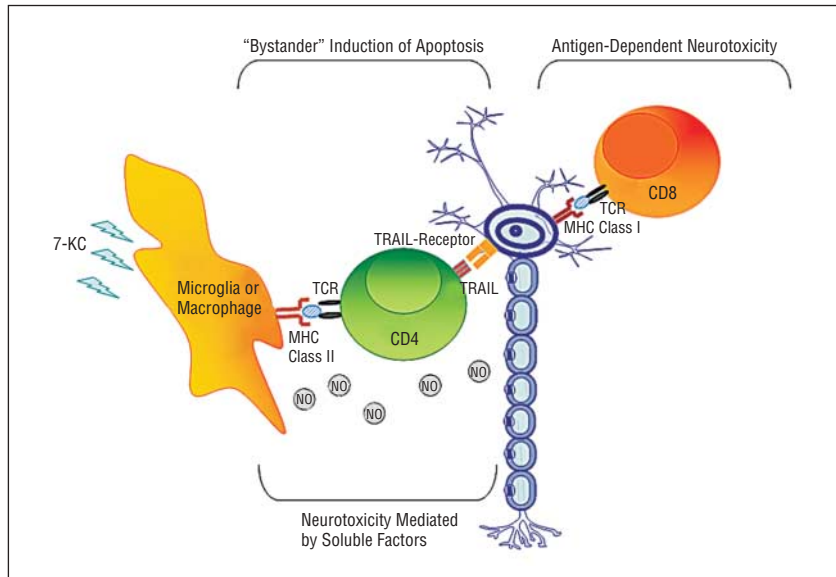
### Neuronal Damage as an Outcome Determiner of Meningoencephalitis

Despite state-of-the-art antibiotic therapy, survivors of bacterial meningitis have diverse neurological symptoms, including seizures, motor deficits, hearing loss, and cognitive impairment indicative of neuronal pathological features. Extensive neuronal death has been found in the hippocampus, an area of the brain associated with learning and memory.<sup>18</sup> Two major pathways are thought to be responsible for neuronal damage in experimental models of meningitis: one is triggered directly by bacterial toxins<sup>19</sup>; and the other is indirect, initiated by an intense inflammatory response by the host (mainly neutrophils) into the CSF and subsequent neuronal death.<sup>18</sup> This immune reaction presumably contributes to an unfavorable outcome, because adjuvant treatment with anti-inflammatory corticosteroids, or blocking leukocyte invasion into the CSF, reduces inflammation and neurological deficits in meningitis. Moreover, bacteria release unmethylated CG dinucleotide motif-rich DNA, which in turn has potent capacities to induce microglia-mediated neurotoxicity via the toll-like receptor 9.<sup>20</sup>

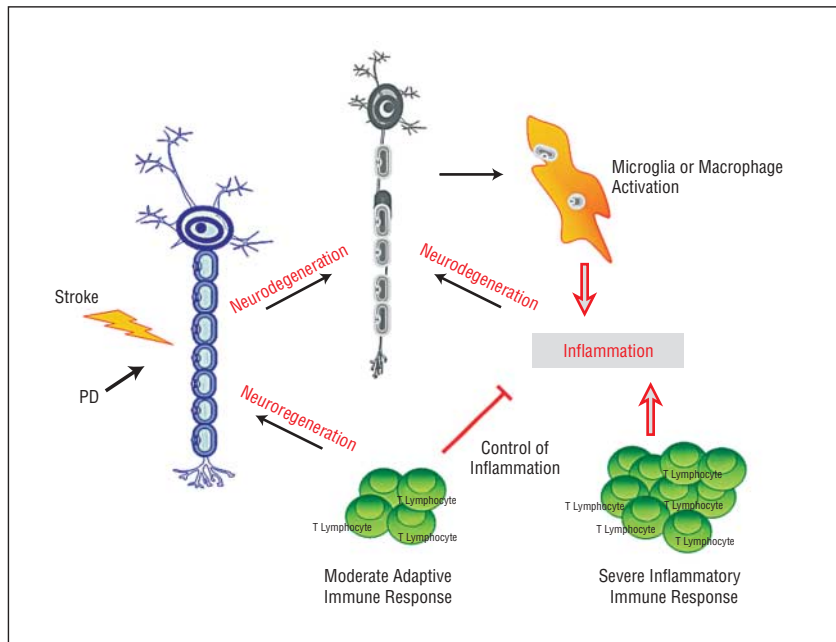
### “SECONDARY” NEUROINFLAMMATION IN NEURODEGENERATIVE DISEASES

#### Inflammation Promotes Stroke, and Stroke Suppresses Immune Defense

In stroke, the critical contribution of inflammatory processes to tissue damage has been recognized (Figure 2). Several studies show that immuno-



**Figure 1.** Neurodegeneration in multiple sclerosis (MS): in MS, neuronal damage could be induced directly by cytotoxic CD8<sup>+</sup> T lymphocytes recognizing antigens presented by major histocompatibility complex (MHC) class I molecules on neurons in the inflamed central nervous system (antigen-dependent neurotoxicity). CD8<sup>+</sup> T lymphocytes might not be only responsible for injury, but may also exert anti-inflammatory functions. On the other hand, activated CD4<sup>+</sup> T lymphocytes have the capacity to kill neurons in a bystander way, independent of antigen presentation, using, for instance, the tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)/TRAIL-receptor system. Neuronal dysfunction and damage also may be mediated by soluble factors, such as nitric oxide (NO) from, for example, activated macrophages or microglia. 7-KC indicates 7-ketocholesterol; and TCR, T-lymphocyte receptor.



**Figure 2.** Inflammation in neurodegenerative diseases: primary neurodegeneration occurring in the course of classic noninflammatory central nervous system disorders, such as stroke or Parkinson disease (PD), might represent the first step of a subsequent inflammatory cascade initiated, for instance, by activated microglia. Inflammation maintained by innate and adaptive immunity could, in turn, promote further neuronal damage. In contrast, a moderate immune response might be beneficial in these disorders by controlling inflammation and promoting neuroregeneration.

suppression or selective targeting of the underlying molecular players may reduce ischemic brain damage. A prominent role has been suggested for interleukin (IL) 1, which mediates neuronal damage in different rodent

models of ischemia.<sup>21</sup> Based on its pronounced neuroprotective effects, the IL-1 receptor antagonist was recently tested in a randomized, double-blind, placebo-controlled, pilot trial<sup>22</sup> in patients with acute stroke. Post hoc

exploratory analysis revealed a better outcome in patients with cortical infarcts, supporting the idea of specific neuroprotection on IL-1 blockade.<sup>21</sup> After acute, persistent, vascular occlusion, necrosis of neurons is the predominant damage mechanism within the affected vascular core territory. However, within the ischemic penumbra and in milder injury, neuronal demise is mediated by apoptosis.<sup>23</sup> Neuronal apoptosis may be induced by metabolic factors (ie, oxygen and glucose deprivation resulting in mitochondrial triggering of cell suicide) and by the action of death-inducing ligands. Indeed, in a rodent stroke model, the expression of TRAIL and the CD95 ligand was found in the apoptotic areas of the postischemic brain. The immunosuppressant FK506 prevented postischemic expression of these death-inducing ligands in vivo and protected against neurodegeneration.<sup>24</sup> In contrast, neuronal damage caused by focal cerebral ischemia or epileptic seizures is enhanced in the absence of the tumor necrosis factor receptors, indicating a more neuroprotective function of tumor necrosis factor. In fact, autoreactive myelin-specific T lymphocytes can also reduce the infarct size,<sup>25</sup> indicating a beneficial role for this part of the immune response, termed *benign autoimmunity*. This observation parallels findings of protection or repair by a mild autoimmune reaction (Figure 2). Conversely, stroke has an effect on the immune system leading to a generalized immunosuppressive state after the immediate insult,<sup>26</sup> again emphasizing the cross talk between the CNS and the immune system.

### Inflammation as a Pacemaker in AD

Although classic disease concepts state that AD is the prototypical primary neurodegenerative disease, the plethora of recent studies demonstrating the critical contribution of the immune system in AD<sup>27</sup> and new immunological therapeutic approaches has prompted a radical paradigm shift. The evidence is based on the following factors: the detection of potent inflammatory molecules, such as cytokines, chemokines, and complement factors, in the CSF, and

in plaques, from patients with AD<sup>27</sup>; the genetic association with inflammatory molecules; and the reduction of disease risk by unspecific anti-inflammatory therapy uncovered in epidemiological studies. It is believed that discrete degenerative processes at the beginning of AD, such as the deposition of highly insoluble A $\beta$  and neurofibrillary tangles, damage neurons and provide clear inflammatory stimuli to local microglia. While the precise immunological and neurodegenerative sequence of events leading to final neuronal loss is not yet known, the induction of a specific immune response by immunization with an A $\beta$  segment markedly reduced pathological features in different transgenic animal models of AD.<sup>28</sup> Consequently, a clinical trial using a sequence from A $\beta$  (AN-1792) in conjunction with a T-lymphocyte-stimulatory adjuvant was initiated to treat AD. However, the trial had to be discontinued, because some patients developed symptoms consistent with meningoencephalitis. A postmortem histological examination of those with meningoencephalitis revealed reduction of cortical plaques and deposition of antibodies in 2 patients, with infiltration of CD4<sup>+</sup> and CD8<sup>+</sup> T lymphocytes and marked macrophage infiltration into the cerebral white matter, indicating a T-lymphocyte-mediated beneficial autoimmune phenomenon.<sup>29</sup>

### Signs of Inflammation in PD and HD

Although still under debate, PD and HD are primarily characterized by limited topical neurodegeneration. Macrophages and microglia were reported to be activated not only in autopsy results of patients with idiopathic PD and HD but also on *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) intoxication in humans and mice with a parkinsonian syndrome thereafter (Figure 2). Similarly, accumulation of reactive microglia in the direct vicinity of pyramidal neurons with HD-positive nuclear inclusions was found at early and progressive stages in the HD-affected brain. Recently, it has been reported that glatiramer acetate, a myelin analogue approved for

MS therapy, is effective in the experimental MPTP-induced PD animal model, because it suppresses microglial activation within the substantia nigra.<sup>30</sup> This process was associated with a local T-lymphocyte accumulation and led to significant dopaminergic neuronal protection, demonstrating that targeted immunomodulation is beneficial in the animal model of PD (Figure 2). On the other hand, systemic inflammation increases the risk of developing PD, because anti-inflammatory treatment for other reasons, such as rheumatoid arthritis, lowers the risk of PD.

### RELEVANCE TO THE PRACTICE OF NEUROLOGY

Practicing neurologists should consider the therapeutic implications of the inflammatory aspects of classic neurodegenerative disorders and of the neurodegenerative aspects of primary inflammatory conditions. In this context, treatment of inflammatory disorders of the brain, such as MS, should not only challenge inflammation but also prevent neuronal damage and promote neuronal degeneration. On the other hand, as mentioned previously, blockade of the inflammatory pathway, such as IL-1-mediated inflammation, seems to have a beneficial effect in stroke, and systemic anti-inflammatory treatment diminishes the risk of developing AD or PD. However, it must be taken into account that, to some extent, inflammation could have a protective role and promote regeneration of damaged neurons. We do not yet know how to achieve a "balanced" inflammation. Because some novel anti-inflammatory treatment might have detrimental consequences, carefully monitoring disease progress in patients treated with this category of drugs is indispensable.

### RELEVANCE TO THE STUDY OF NEUROSCIENCES

As reviewed herein, classic neuroinflammatory CNS diseases are characterized by substantial neuronal damage. Surprisingly, injury to neuronal structures in the CNS in the context of noninflammatory brain diseases brings an immune response in its wake, and there is grow-



ing evidence that immunomodulatory therapies are often beneficial for primary neurodegenerative diseases. This is most obvious in the case of the myelin analogue glatiramer acetate, which seems to be beneficial in various experimental settings, from primary degeneration to autoimmune demyelination. The explanations for these effects range from induction of regulatory immune cells to arousal of “benign autoimmunity.” In any case, it is certain that the immune response has the potential to modulate neurodegeneration, as indicated by the pivotal vaccination trials in AD. Concerning the other target structure in the brain—the oligodendrocytes and myelin sheaths—dysfunction or damage can result in inflammation. Apparently, the context of the CNS insult defines the interplay of the nervous and immune systems and the final outcome. From the data discussed herein, it may be concluded that in a variety of neurological diseases the initial triggers differ significantly, while the subsequent pathways involving inflammatory processes and causing brain damage share certain pathological mechanisms. Targeting these processes arising at the interface of neuroimmunology and neurobiology may help to develop more selective therapies in neurology.

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