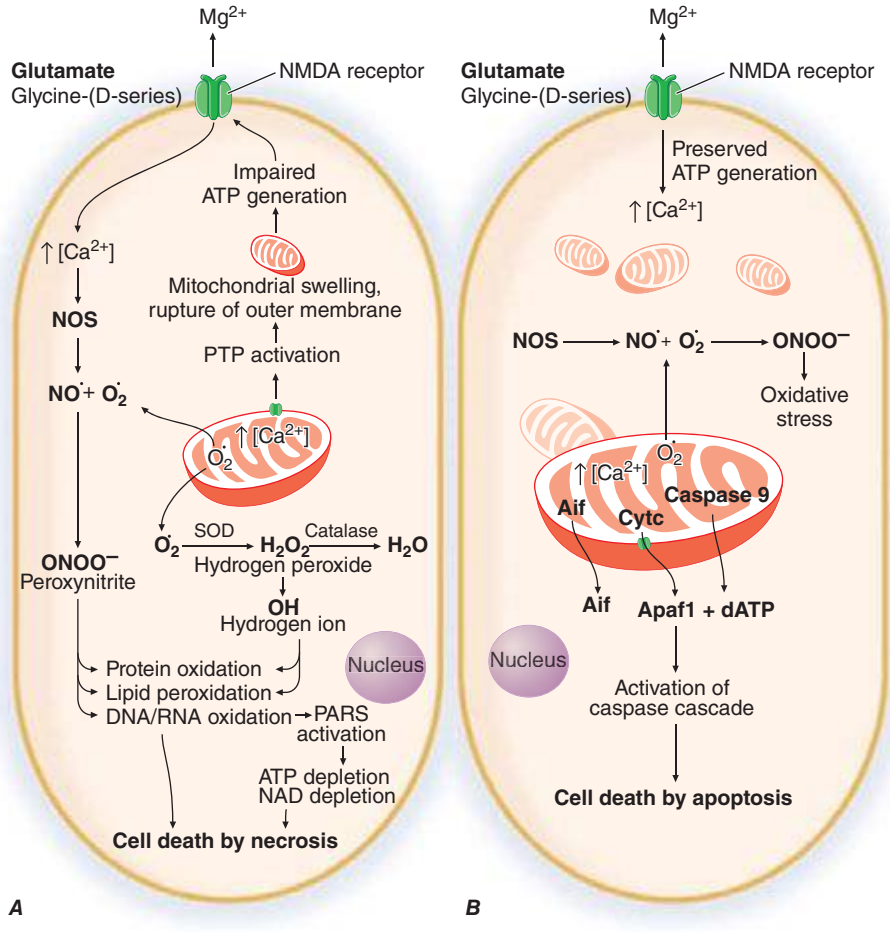

FIGURE 444e-2 **Involvement of mitochondria in cell death.** A severe excitotoxic insult (***A***) results in cell death by necrosis, whereas a mild excitotoxic insult (***B***) results in apoptosis. After a severe insult (such as ischemia), there is a large increase in glutamate activation of *N*-methyl-D-aspartate (NMDA) receptors, an increase in intracellular Ca^{2+} concentrations, activation of nitric oxide synthase (NOS), and increased mitochondrial Ca^{2+} and superoxide generation followed by the formation of $ONOO^-$. This sequence results in damage to cellular macromolecules including DNA, leading to activation of poly-ADP-ribose polymerase (PARS). Both mitochondrial accumulation of Ca^{2+} and oxidative damage lead to activation of the permeability transition pore (PTP) that is linked to excitotoxic cell death. A mild excitotoxic insult can occur due either to an abnormality in an excitotoxicity amino acid receptor, allowing more Ca^{2+} flux, or to impaired functioning of other ionic channels or of energy production, which may allow the voltage-dependent NMDA receptor to be activated by ambient concentrations of glutamate. This event can then lead to increased mitochondrial Ca^{2+} and free radical production, yet relatively preserved ATP generation. The mitochondria may then release cytochrome c (Cytc), caspase 9, apoptosis-inducing factor (Aif), and perhaps other mediators that lead to apoptosis. The precise role of the PTP in this mode of cell death is still being clarified, but there does appear to be involvement of the adenine nucleotide transporter that is a key component of the PTP.

propensity to be targeted as autoantigens in autoimmune demyelinating disorders (Fig. 444e-2).

Specification to oligodendrocyte precursor cells (OPCs) is transcriptionally regulated by the *Olig 2* and *Yin Yang 1* genes, whereas myelination mediated by postmitotic oligodendrocytes depends on a different transcription factor, *myelin gene regulatory factor (MRF)*. It is noteworthy that in the normal adult brain, large numbers of OPCs (expressing PDGFR-α and NG2) are widely distributed but do not myelinate axons, even in demyelinating environments such as in lesions of MS. Several families of molecules have now been identified that regulate oligodendrocyte differentiation and myelination, including LINGO-1, PSA-NCAM, hyaluronan, Nogo-A, the Wnt pathway, notch signaling (and its receptor Jagged), and the retinoic acid receptor RXRγ; all are inhibitory, with the exception of RXRγ, which is excitatory. All are also potential targets for myelin repair therapies, and a monoclonal antibody against LINGO-1 is in clinical testing for remyelination in MS. Very recently, a series of observations has called into question the traditional concept that axon-derived cues are always required for myelination to occur. Fixed (i.e., dead) axons could be efficiently myelinated by oligodendrocytes in vitro, as could artificial polystyrene nanowires of a similar diameter. This led to development of new high-throughput screening assays based on myelination of polystyrene nanowires to identify compounds that could promote myelination.

Macrophages and microglia represent the major cell types in the nervous system responsible for antigen presentation and innate immunity. Brain macrophages are derived from either hematopoietic stem cell–derived bone marrow monocytes or from brain microglia that migrate from the yolk sac early in embryogenesis before the blood-brain barrier is formed. In a murine model of autoimmune demyelination, experimental allergic encephalomyelitis (EAE) (Fig. 444e-3), macrophages derived from bone marrow monocytes, but not microglia, were found to represent the critical population that initiated inflammatory demyelination at paraxonal regions near nodes of Ranvier. An additional, unexpected role for brain microglia was also identified in the regulation of neural circuits through pruning of excitatory synapses and control of dendritic spine densities; mice depleted of microglia during development exhibited a variety of cognitive learning and behavioral deficits, including abnormal social behaviors. Remarkably, depletion of microglia in adult mice by administration of a selective inhibitor of colony-stimulating factor receptor 1 (CSFR1) was followed by their rapid repopulation, suggesting that a pool of resident microglial precursor cells may exist throughout the CNS.