severe hypoxia, neurons die quite rapidly. When the insult is less severe, some neurons can survive and some local growth occurs. Because central axons have little ability to regenerate, the key to recovery from brain injury lies with the complex cellular events pertinent to the survival of neurons (see Chapter 23) that have not been killed outright, and whose processes remain relatively intact.

Cellular and Molecular Responses to Brain Injury

There are two major reasons for the differences between successful peripheral regeneration and the limited regeneration in the CNS. First, damage to brain tissue tends to engage the mechanisms that lead to necrotic and apoptotic cell death for nearby neurons whose process have been severed. Second, the cellular changes at the site of injury do not recapitulate developmental signaling that supports growth. Instead, there is a combination of glial growth and prolifera-

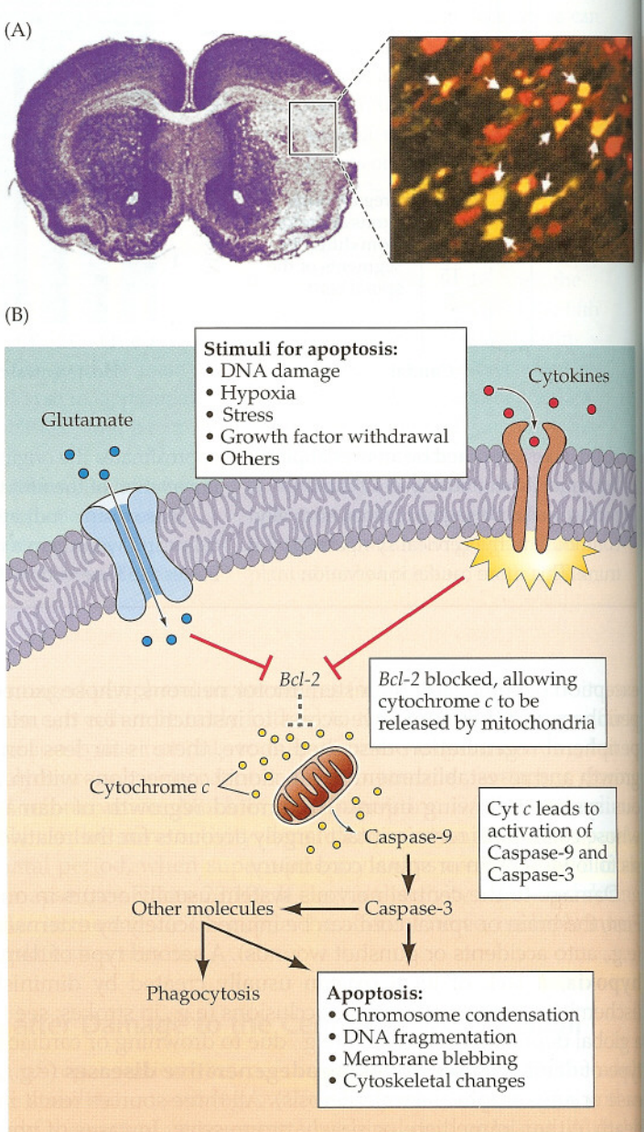

Figure 25.8 Consequences of hypoxia/ischemia in the mammalian brain. (A) Section through the brain of a 7-day-old mouse in which the carotid artery was transiently constricted. Nissl stain (see Chapter 1) was used to visualize cell bodies. The lighter region (i.e., little or no staining) shows the extent of cell damage and loss caused by this brief deprivation of oxygen. Cells in the higher magnification image were stained for the neuronal marker Neu-N (red) and for activated caspase-3, indicative of neurons undergoing apoptosis. (B) Model of the primary mechanism for neuronal apoptosis after injury. Apoptosis can be elicited by excitotoxicity via excess glutamate, and by the binding of inflammatory cytokines to receptors in the neuronal membrane. In addition, loss of neuronal connections to a target and resultant deprivation of trophic support can initiate apoptosis. Any or all of these stimuli, once present, result in the removal of the anti-apoptotic gene *Bcl-2*. Cytochrome *c* is then released from mitochondria, activating caspase-3 and obligating the cell to apoptotic death as caspase-3 stimulates destructive changes in downstream molecules. (A from Back et al., 2002.)

tion, and microglial activity (microglia have immune functions that lead to local inflammation) that actively inhibits growth as well as upregulation of growth-inhibiting molecules related to the chemorepellent factors that influence axon trajectories during development. Again, why these inhibitory phenomena occur is a central question for understanding the lack of successful regeneration in the brain.

One of the most striking differences in the consequences of CNS versus peripheral nerve cell damage is the extent of cell death that occurs after direct damage to the brain (Figure 25.8A). Neuronal cell death in the CNS is seen regardless of the type of damage (traumatic, hypoxic, or degenerative). It has been studied most extensively in brains where hypoxia has occurred due to vascular occlusion (e.g., stroke, vascular accidents, and asphyxiation). In such cases, there is a clear loss of cells in the hypoxic region. Where such cell loss has occurred, there is also enhanced activation of **caspase-3**, an enzyme that, when activated, obligates a cell to die via **apoptosis** (Figure 25.8B). This genetically regulated mechanism can be elicited by growth factor deprivation, hypoxia, or by DNA damage and other cellular stress. The transection of axons presumably can lead to growth factor deprivation by removing the target source for the parent neurons. DNA damage and cellular stress (including changes in oxidative metabolism) have been suggested to underlie some neurodegenerative diseases.

A major source of cellular stress is glutamatergic overstimulation caused by bursts of abnormal activity arising after local brain damage. Such overstimulation can also arise from epileptogenic foci and the seizure activity generated at these sites. This elevated activity and its consequences are referred to as **excitotoxicity**, and if unchecked it can lead to neuronal cell death (see Box 6D). Following injury or seizure, excessive amounts of neurotransmitters are released. This enhanced signaling modifies the effectiveness of members of the Bcl-2 family of anti-apoptotic molecules that normally oppose changes in mitochondrial function that reflect oxidative stress. Diminished *Bcl-2* activity allows cytochrome *c* to be liberated from mitochondria. Once in the cytoplasm, cytochrome *c* facilitates cleavage of caspase-3, activating this enzyme. Activated caspase-3 can then cause the fragmentation of nuclear DNA, membrane and cytoskeletal changes, and ultimately cell death (Figure 25.8B). Thus, one of the key determinants of the long-term effects of damage to adult neural tissue is the extent to which the damage activates apoptosis.

As might be expected from events in the periphery, glial cells found at the site of injury contribute to the degenerative and regenerative processes that occur after brain damage. All three glial classes—astrocytes, oligodendroglia, and microglia—display altered properties following brain injury (Figure 25.9). In addition, glia seem less susceptible to the stimuli that result in apoptosis. Most brain lesions cause limited proliferation of otherwise quiescent glial precursors, as well as extensive growth of existing glial cells within or around the site of injury. These reactions lead to the glial "scarring" referred to earlier, accompanied by increased secretion of a number of signals including transforming growth factor (TGF), fibroblast growth factor (FGF), tissue necrosis factor alpha (TNF-α), interleukins, interferon-γ, and insulin-like growth factor-1 (IGF-1). Depending on the cellular target (neuronal or glial), these signals (some of which are **cytokines**, most of which serve signaling roles in the immune system) can either promote cell death and phagocytosis (see Figure 25.8B), or provide protective signals for remaining nerve cells. Depending on the type of injury and the time elapsed since its occurrence, the **reactive glia** alter the relationships between remaining nerve cells and the glial environment, or they become the dominant cell type in the region of damage by replacing lost neurons and degenerated processes, resulting in the long-term glial scar.

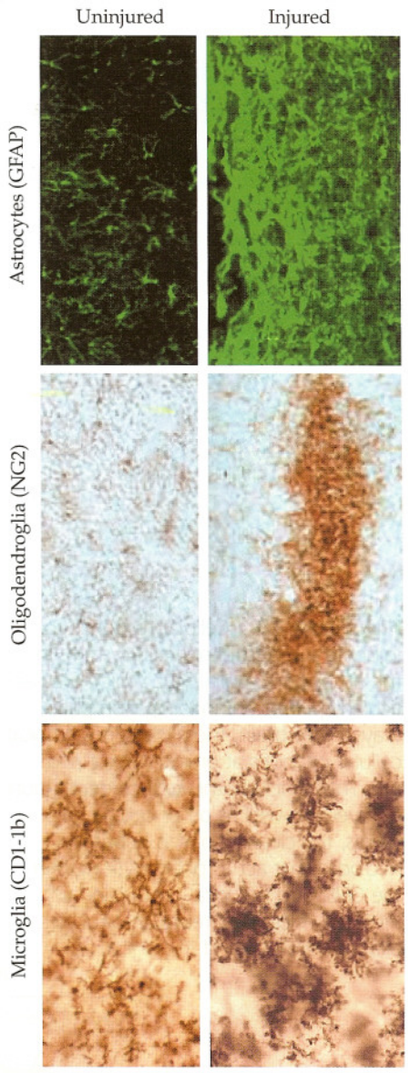

Figure 25.9 The reaction of the three major classes of glia in the central nervous system to local tissue damage. In each case, there is growth and change in expression of molecules normally associated with each cell class. (Top) Astrocytes labeled to visualize glial fibrillary acidic protein (GFAP) both before and after injury. (Center) The molecule NG2, notably present in glial scar tissue, is visualized here in oligodendroglial precursors and immature oligodendrocytes. (Bottom) CD1-1b, a marker for microglia. (Top from McGraw et al., 2001; center from Tan et al., 2005; bottom from Ladeby et al., 2005.)