In recent years substantial advances have taken place in understanding the mechanistic pathways mediating neuronal cell death in a variety of neurologic diseases. Since the central nervous system (CNS) has little, if any, power of functional neuronal regeneration, prevention of neuronal cell death is an important target of modern neurotherapeutics. A detailed understanding of the mechanisms mediating neuronal cell death is required to effectively slow the progression of neurologic diseases featuring apoptosis. Increasing evidence demonstrates that blocking cell death pathways in cells otherwise fated to die (ie, following stroke, trauma, or in neurodegenerative diseases) improves neurologic outcome.1-7

Broadly, cells can die by 1 of 2 mechanisms: necrosis or apoptosis. Necrotic cell death is a more passive form of cell death, where the stimulus itself alters cell homeostasis resulting in its death. On the other hand, apoptosis (also known as programmed cell death) is a more active and physiologic form of cell death, where the death stimulus triggers the cellular suicide program, and it is this program (and not the stimulus itself) that mediates the demise of the cell.8

Pathways mediating apoptosis have been preserved through evolution. Specific mediators of apoptosis were first identified through elegant genetic studies of the nematode Caenorhabditis Elegans. Several genes required for cell death were identified in the worm (ced-3 and ced-4).9 The interleukin (IL) 1β converting enzyme (ICE) was the first mammalian gene identified with sequence homology to ced-3.10 Extensive studies have demonstrated that ICE is an important mediator of apoptosis in mammalian cells and a functional homolog of ced-3.11 Since the identification of ICE as a mediator of apoptosis, an additional 13 mammalian homologs have been identified. This family of cell death cysteine proteases has been called caspases. In recent years, caspases have been identified as central mediators of cell death in a variety of neurologic diseases. The role of caspases, in particular caspase 1, in neurologic diseases will be the focus of this review.

Following exposure to an apoptotic death–promoting stimulus, a tightly regulated cascade becomes activated executing the death of the cell. Caspase activation results in cell death by destroying molecules required for cell survival and activating others mediating the suicide program. Caspase 1 and caspase 3 are the 2 caspase family members for which most information has been generated. Caspase 1, the founding member of the caspase family, is responsible for cleavage of pro-IL-1β to the mature and active form of the cytokine.11 Evidence indicates that following caspase 1 activation, binding of mature IL-1β to its type 1 receptor plays an important role mediating neuronal cell death.12 Since caspase 1 is required in mice (and likely also in humans) to process pro-IL-1β, detection of mature IL-1β indicates activation of caspase 1.13 We have used detection of mature IL-1β as a sensitive and specific method to ascertain caspase 1 activation. Caspase 3, another important mediator of apoptosis, seems to be the end-
pathway effector for most apoptotic pathways. Caspase 3 activates the DNase responsible for the cleavage of DNA into the classic DNA fragments detected on agarose gels and by TUNEL staining. Caspase 1 and caspase 3 activation have been demonstrated in a variety of neurologic diseases.

Central nervous system degeneration may be broadly classified as acute or chronic. In acute neurologic diseases (ie, stroke and traumatic brain and spinal cord injury), the greatest magnitude of cell death occurs shortly following the insult (Figure 1). However, cell death is detected for up to 3 weeks following the initial insult. In chronic neurologic diseases (eg, amyotrophic lateral sclerosis [ALS], Huntington disease [HD], and Alzheimer disease), the presence of the apoptotic stimulus is constant, and therefore cell death occurs over a period of years. Interestingly, caspase-mediated pathways are shared as part of the pathogenic progression in acute and chronic neurodegeneration.

**ACUTE CELL DEATH DISEASES**

Of the acute CNS disorders featuring apoptotic cell death, cerebral ischemia is the most thoroughly studied and best understood. Other diseases in the acute cell death category include traumatic brain injury and spinal cord injury. I will use ischemia as the prototype disease in the acute category; however, similar pathways to play a role in the other acute cell death diseases as well. Following ischemia, both necrotic and apoptotic cell death are detected. Necrotic death occurs at the core of the infarct area where the insult is most severe. However, in the ischemic penumbra, where the ischemic insult is not as severe, apoptotic mechanisms are triggered and TUNEL-positive cells are clearly identified. The speed of detecting apoptotic bodies bears direct correlation to the magnitude of the ischemic insult. Following 2 hours of focal ischemia, apoptotic cells are detected within 6 hours. On the other hand, following 30 minutes of transient global ischemia, apoptotic cells are not detected for 24 hours and are detected up to 2 weeks following the insult. This extended time frame of apoptotic cell death occurs not only in ischemia but also in CNS trauma. These results provide very important evidence demonstrating that the activation of cell death pathways is not an all-or-none phenomenon, but rather a graded process where the magnitude of the activation of the apoptotic pathways is directly proportional to the magnitude of the effector death cascade. Initial activation of caspase pathways is not an irreversible process, and it does not always lead to cell death. Therefore, if intervention occurs early enough, cell death can be aborted, thus rescuing neuronal populations and improving neurologic outcome.

Following ischemic or traumatic injury, caspase 1 and caspase 3 are activated. Three main approaches have been used to evaluate whether caspase activation plays a functional role mediating cell death and neurologic deterioration. First, intracerebroventricular administration of synthetic caspase peptide inhibitors has been used as a pharmacologic approach to block caspase activation. Second, my colleagues and I have used a transgenic mouse expressing a dominant negative mutant of caspase 1 under the control of the neuron specific enolase promoter (NSE-M17Z). We demonstrated that this construct is a functional caspase-1–dominant negative inhibitor. This construct might also inhibit additional caspases. The third approach involves the use of caspase-1–deficient mice. Reduction of tissue damage and improved neurologic outcome occurs in rodents treated with caspase peptide inhibitors, in mice expressing the caspase-1–dominant negative inhibitor, and in caspase-1–deficient mice. These data provide strong evidence of an important functional role of the caspase family in mediating tissue injury and neurologic dysfunction following an ischemic insult.

These findings are not particular to ischemic brain damage; similar protection is afforded by caspase peptide inhibitors in a small-bowel ischemic paradigm and following traumatic brain injury. These results taken together demonstrate that caspase-mediated cell death is a shared common pathway playing an important functional role following CNS trauma and ischemia.

**CHRONIC CELL DEATH DISEASES**

Abundant evidence implicates caspase-driven apoptotic pathways in the pathogenesis of several chronic neurodegenerative diseases. This evidence has been generated by using a variety of complementary approaches, including evaluating human tissue and using transgenic mouse and neurotoxin models and in vitro models. I will discuss the evidence linking caspase activity with the pathogenesis of 2 neurodegenerative diseases: ALS and HD. Evidence linking caspase to additional neurodegenerative diseases also exists.
Amyotrophic Lateral Sclerosis

Apoptotic cell death has been detected in spinal cords of patients with ALS. In addition, clear evidence for caspase 1 activation and apoptotic cell death has been detected using in vitro models of ALS. Mutant SOD-1–mediated apoptotic cell death in vitro is effectively inhibited by synthetic peptide caspase inhibitors. These results provide evidence for the activation of caspases by the mutant SOD-1 gene. Further specific in vivo evidence for caspase 1 activation was found using a transgenic mouse model of familial ALS. Extended survival occurs in this ALS mouse model when the mouse is crossed with a transgenic mouse expressing either the caspase 1–dominant negative inhibitor or Bcl-2. Also recently demonstrated has been a delay in disease progression and mortality in ALS mice treated with a caspase inhibitor.

Huntington Disease

Huntington disease is 1 of 8 diseases where the etiologic mutation has been determined to be a CAG expansion encoding for an abnormal polyglutamine stretch in the gene identified as a cause for the disease. Abundant evidence links several of these diseases with aberrant caspase function. Interestingly, several of these disease gene products are themselves caspase substrates. The particular relation of caspase-mediated cleavage of these proteins with disease progression remains controversial. However, the resultant cleavage fragments seem to have a toxic gain of function, providing a direct link between the caspase family and polyglutamine diseases. Much information exists linking caspase apoptotic pathways with the progression of HD. Apoptotic cell death has been clearly demonstrated in the striatum of humans with HD as well as in transgenic mouse models. In addition, caspase 1 activation occurs in brains of humans and mice with HD. Interestingly, huntingtin itself is cleaved by caspase 1 and caspase 3. Generation of these toxic fragments seems to be required for the pathogenic disease progression as well as for the formation of neuronal intranuclear inclusions (Figure 2), which are detected in brain specimens of both humans with HD and mouse models. It also occurs in human HD brain specimens. In addition, inhibition of caspase 1 function improves neurologic outcome in the above-mentioned diseases. Since caspase-mediated apoptotic pathways are shared between acute and chronic neurologic conditions, effective therapies for one might be effective for others. However, differences will clearly exist in designing effective therapies for the treatment of acute and chronic conditions. As our understanding of the specific mechanistic pathways mediating neurodegeneration increases, we approach being able to develop rational targeted pharmacotherapy for the treatment of diseases featuring caspase-driven apoptosis.

CONCLUSIONS

Caspase 1 activation occurs in models of cerebral ischemia and trauma, ALS, and HD. It also occurs in human HD brain specimens. In addition, inhibition of caspase 1 function improves neurologic outcome in the above-mentioned diseases. Since caspase-mediated apoptotic pathways are shared between acute and chronic neurologic conditions, effective therapies for one might be effective for others. However, differences will clearly exist in designing effective therapies for the treatment of acute and chronic conditions. As our understanding of the specific mechanistic pathways mediating neurodegeneration increases, we approach being able to develop rational targeted pharmacotherapy for the treatment of diseases featuring caspase-driven apoptosis.

Figure 2. Cellular pathogenesis in Huntington disease. Expression of mutant huntingtin (m-htt) generates a toxic reaction within a specific population of cells. The cause for the vulnerability of certain cell types is not understood. As a certain level of “cell toxicity” is reached, and caspase 1 is activated, caspase 1 may directly or indirectly activate caspase 3, and both of these caspases then cleave the full-length htt molecule generating the toxic fragments (m-htt fragment). As a detrimental feedback loop m-htt fragments exacerbate cell toxicity and accelerate the formation of neuronal intranuclear inclusions (NIIs) causing further caspase activation. Progression of cell dysfunction (in part manifested as a decreased number of specific neuroreceptors) and cell death translate at the organismal level to symptomatic disease progression.

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REFERENCES


