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Forum Review

Neuronal Life-and-Death Signaling, Apoptosis, and Neurodegenerative Disorders

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ABSTRACT

When subjected to excessive oxidative stress, neurons may respond adaptively to overcome the stress, or they may activate a programmed cell death pathway called apoptosis. Apoptosis is characterized by alterations in mitochondria and the endoplasmic reticulum and activation of cysteine proteases called caspases. Increasing evidence suggests that apoptotic biochemical cascades are involved in the dysfunction and death of neurons in neurodegenerative disorders such as Alzheimer's, Parkinson, and Huntington's diseases. Studies of normal aging, of genetic mutations that cause disease, and of environmental factors that affect disease risk are revealing cellular and molecular alterations that may cause excessive oxidative stress and trigger neuronal apoptosis. Accumulation of self-aggregating proteins such as amyloid β-peptide, tau, α-synuclein, and huntingtin may be involved in apoptosis both upstream and downstream of oxidative stress. Membrane-associated oxidative stress resulting in perturbed lipid metabolism and disruption of cellular calcium homeostasis may trigger apoptosis in several different neurodegenerative disorders. Counteracting neurodegenerative processes are an array of mechanisms including neurotrophic factor signaling, antioxidant enzymes, protein chaperones, antiapoptotic proteins, and ionostatic systems. Emerging findings suggest that the resistance of neurons to death during aging can be enhanced by modifications of diet and lifestyle. *Antioxid. Redox Signal.* 8, 1997–2006.

CELLULAR AND MOLECULAR CHARACTERISTICS OF APOPTOSIS

APOPTOSIS IS A FORM OF PROGRAMMED CELL DEATH that occurs normally in most tissues during embryonic and postnatal development in mammals and in many lower organisms as well. Apoptosis also occurs in proliferative tissues of adult organisms. One defining feature of a cell undergoing apoptosis is that it dies alone, usually among healthy neighboring cells (Fig. 1). In this regard, apoptosis is a mechanism by which dysfunctional or damaged cells are removed from a tissue without adversely affecting other cells in the tissue. An understanding of apoptosis is central to many different human diseases. For example, abnormal resistance to apoptosis is an important aspect of cancer cells, whereas unwanted susceptibility of cells to apoptosis occurs in myocardial infarction and stroke. Because of its fundamental importance for normal tissue homeostasis and its involvement in a range of diseases, the molecular mechanisms of apoptosis have been of intense interest for many biologists, biomedical scientists, and clinicians. A PubMed search with the keyword "apoptosis" retrieves more than 110,000 articles, and a search with "apoptosis" and "neurons" reveals more than 8,000 articles. Many excellent recent review articles are found on the topic of neuronal apoptosis (12, 80, 110, 146), and I therefore only briefly review key aspects of apoptosis.

Neurons undergoing apoptosis in response to firmly established triggers, such as neurotrophic factor deprivation or exposure to kinase inhibitors such as staurosporine, shrink, develop blebs of their plasma membrane, exhibit nuclear chromatin condensation and fragmentation, and largely retain membrane integrity and internal structure of organelles including mitochondria and the endoplasmic reticulum (ER). In many cases, changes in the mitochondria and ER are pivotal

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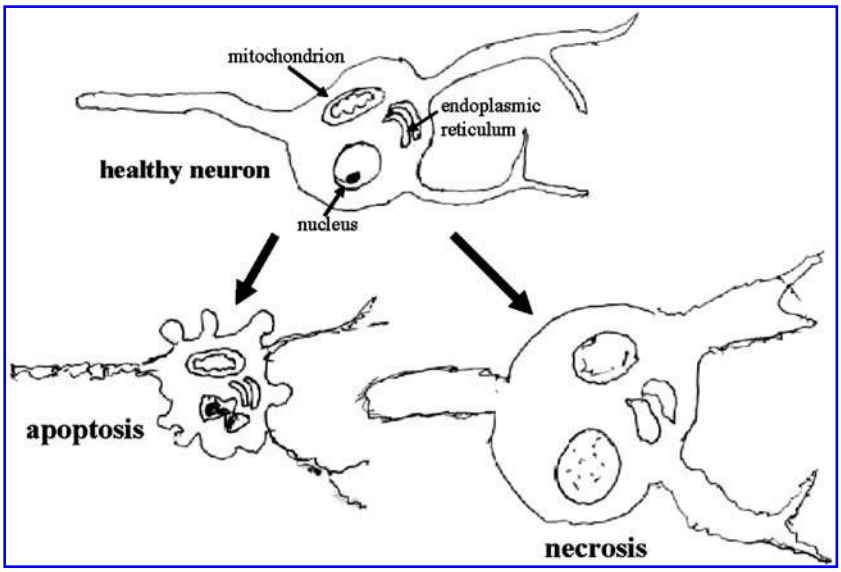

FIG. 1. Distinguishing features of apoptosis and necrosis. Morphologic changes that occur during apoptosis include cell shrinkage, blebbing of the plasma membrane, and nuclear chromatin condensation and fragmentation with preservation of the structure of mitochondria and the endoplasmic reticulum. During necrosis, cells swell, mitochondria and endoplasmic reticulum lose their structure and become dysfunctional, and the nuclear membrane becomes disrupted. Necrosis is further distinguished from apoptosis, in that cells die *en masse*, whereas apoptosis typically occurs in individual cells within a population of surviving neighbors.

early events in the apoptotic cascade (83, 123). Examples of premitochondrial events in apoptosis include upregulation and/or mitochondrial translocation of proapoptotic proteins such as p53, Bax, and Par-4 (Fig. 2). Within the mitochondria, permeability transition pores (PTP) form in the mitochondrial membranes, resulting in the release of cytochrome *c* and/or apoptosis-inducing factor (AIF) into the cytosol. Subsequently, cysteine proteases called caspases (caspases 9 and 3, in particular) are activated, resulting in the cleavage of a range of cytoplasmic, membrane-associated, and nuclear protein substrates. Within the plasma membrane, phosphatidylserine translocates from the inner to the outer leaflet of the phospholipid bilayer, where it serves as a signal for recognition and engulfment of the dying cell by macrophages and microglia.

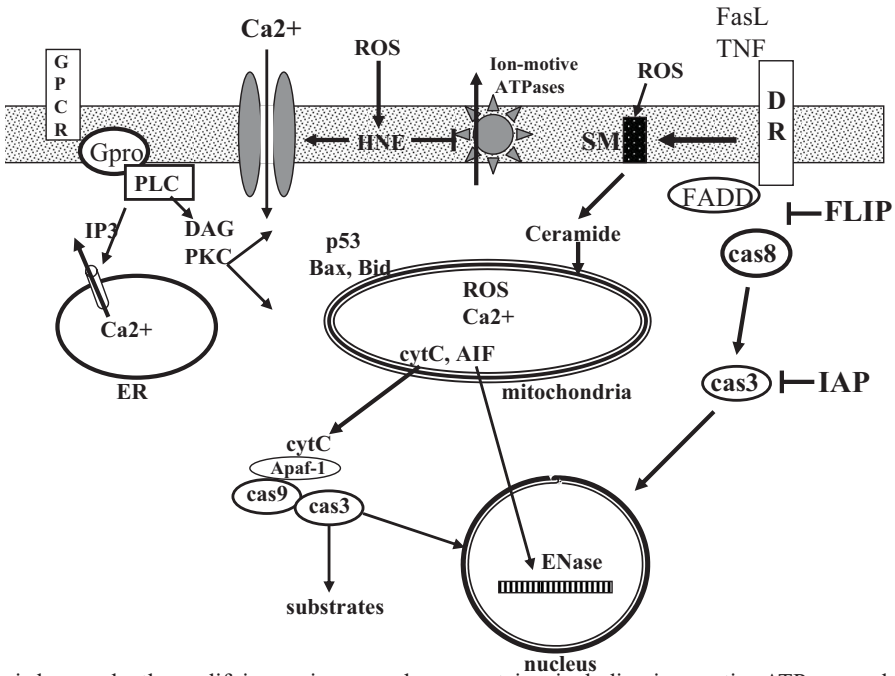

FIG. 2. Examples of plasma membrane–initiated cell death cascades. Many cells, including neurons, express so-called death receptors (DRs). In the example shown, a receptor for Fas ligand (FasL) or tumor necrosis factor (TNF) binds a protein called FADD (Fas-associated death domain), which then recruits and activates caspase 8 (cas8). Caspase 8 then activates caspase-3, which plays a major role in executing the cell-death process. The latter death-receptor pathway can be blocked by the activities of FLIP (FLICE inhibitory protein) and IAPs (inhibitor of apoptosis proteins). Cell death also can be triggered by reactive oxygen species (ROS) that induce membrane-associated oxidative stress. Membrane lipid peroxidation generates the aldehyde 4-hydroxynonenal (HNE), which can induce apoptosis by covalently modifying various membrane proteins, including ion-motive ATPases and calcium channel proteins. Membrane oxidative stress also activates sphingomyelinases, which cleave sphingomyelin (SM), resulting in the production of ceramide, which can trigger apoptosis by inducing mitochondrial membrane-permeability transition. GTP-binding protein-coupled receptors (GPCR) that stimulate GTP-binding proteins (Gpro) and activation of phospholipase C (PLC) can trigger cell death by inducing calcium release from IP3-sensitive ER stores. Once initiated, such cell-death cascades often involve proapoptotic proteins acting at mitochondrial membranes (p53, Bax, and Bid, for example), proteins released from mitochondria (cytochrome *c* and AIF), caspases, and endonucleases (ENase).

In addition to the "mitochondrial pathway" of apoptosis, neuronal apoptosis may occur by the so-called "extrinsic pathway," in which "death receptors" on the cell surface are activated by certain proapoptotic ligands. The latter pathway involves activation of caspase 8, which may directly activate effector caspases such as caspase 3. The occurrence of the events just described (and the ability of caspase inhibitors and inhibitors of protein synthesis to prevent cell death) establishes the cell death as apoptosis.

Several different triggers of neuronal apoptosis have been demonstrated in cell culture and *in vivo*. Examples of specific triggers include the excitatory neurotransmitter glutamate (3), deprivation of neurotrophic factors such as nerve growth factor (NGF), basic fibroblast growth factor (bFGF), and brain-derived neurotrophic factor (BDNF) (16, 22, 112), and nitric oxide (46). Other, more generalized triggers include membrane lipid peroxidation (64); calcium release from the endoplasmic reticulum (9, 18); and accumulation of damaged proteins (31). Brakes on apoptosis include neurotrophic factors, antiapoptotic Bcl-2 family members (72), inhibitor of apoptosis proteins (IAPs; 113), antioxidants (42), calcium-stabilizing proteins (84), and protein chaperones such as the heat-shock proteins (HSPs) and ER chaperones (43).

ANTIAPOPTOTIC CELL LIFE SIGNALING MECHANISMS

The longevity of neurons is remarkable, with many in humans surviving for 10 decades or more. How do neurons avoid apoptosis in the face of aging and changing environmental conditions? A substantial portion of the proteome of a neuron is devoted to prevention of apoptosis. Illustrative of such proteins are those involved in dissipating oxidative stress, chaperoning and degrading proteins, regulating energy metabolism, and maintaining ion homeostasis. Proteins that can prevent apoptosis by decreasing oxidative stress include antioxidant enzymes such as superoxide dismutases (Cu/Zn-SOD and Mn-SOD), catalase and glutathione peroxidase, and mitochondrial uncoupling proteins (55, 60, 133). Proteins that help prevent damage to proteins include chaperones such as heat-shock proteins (HSP-70, HSP-27, HSP-90) and glucose-regulated proteins (GRP-78 and GRP-94) (133, 144), whereas proteins that remove damaged proteins include the enzymes involved in the ubiquitin–proteasome system (19, 57). Among proteins involved in energy metabolism, mitochondrial and plasma membrane redox enzymes, insulin signaling pathway proteins, and sirtuins influence neuronal apoptosis (15, 21, 117). Proteins involved in DNA repair are also likely to serve important antiapoptotic roles under a variety of adverse conditions that can result in DNA damage (40, 67).

Intercellular signaling mechanisms are of considerable importance in sustaining the life of neurons. Several neurotrophic factors have been identified that can prevent apoptosis of neurons, including basic fibroblast growth factor (bFGF), nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), glial cell line–derived neurotrophic factor (GDNF), and insulin-like growth factor-1 (IGF-1) (4, 22, 23, 59, 100). In addition to protecting mature neurons against apoptosis, neurotrophic factors can prevent apoptosis of newly generated neurons produced from neural stem cells (70). Neurotrophic factors may prevent apoptosis by activating kinases such as mitogen-activated protein (MAP) kinases and Akt, and transcription factors such as cyclic AMP response element–binding protein (CREB) and NF-κB (87, 95, 112). Genes modulated by neurotrophic factors include those encoding proteins such as Bcl-2 family members, IAPs, antioxidant enzymes, and calcium-regulating proteins (2, 78, 107).

Hormesis is an important mechanism by which neurons may resist apoptosis. When cells are exposed to sublethal levels of stress (oxidative stress, ischemia, calcium overload, toxins, *etc*.) they often become resistant to being killed by more severe stress (94). This process, which is termed "hormesis" or "preconditioning," involves the activation of stress-signaling pathways that lead to the production of cytoprotective antiapoptotic proteins. For example, exposure of neurons to moderate levels of glutamate-receptor agonists results in calcium influx, activation of CREB and NF-κB, and upregulation of the expression of BDNF and Bcl-2 (8, 58). Ischemic preconditioning is also associated with increased production of neurotrophic factors, protein chaperones, and antioxidant systems (142). Hormesis may be a major mechanism whereby mild stresses such as dietary restriction, physical exercise, and cognitive stimulation protect neurons against apoptosis (54, 86).

APOPTOSIS IN NEURODEGENERATIVE DISORDERS

Increasing evidence indicates that the deaths of neurons that occur in many different neurodegenerative disorders occur by apoptosis or a closely related mechanism. In this section, I briefly review some of the evidence for apoptosis in several of the most common neurodegenerative conditions: Alzheimer's disease (AD), Parkinson disease (PD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), and stroke (Fig. 3). This article is not intended to be a comprehensive review and emphasizes our own findings in this field of investigation. In AD, PD, HD, and ALS, the affected neurons do not die *en masse*, and necrosis is therefore not the mode of cell death (for reviews, see 6, 14, 80, 122). In stroke, neurons in the core (most severely affected) region of the ischemic infarct undergo necrosis—they rapidly swell and lyse. However, neurons in the surrounding region (ischemic penumbra) die more slowly by an apoptosis-like process (121). The present article considers evidence supporting a role for neuronal apoptosis in four chronic neurodegenerative disorders: AD, PD, HD, and ALS. The role of neuronal apoptosis in stroke has been reviewed elsewhere (73, 81, 126, 147) and is not considered further here.

Data from patients

Microscopic and biochemical analyses of brain tissues from AD, PD, and HD patients, and from the spinal cords of ALS patients, have provided evidence that apoptosis of neu-

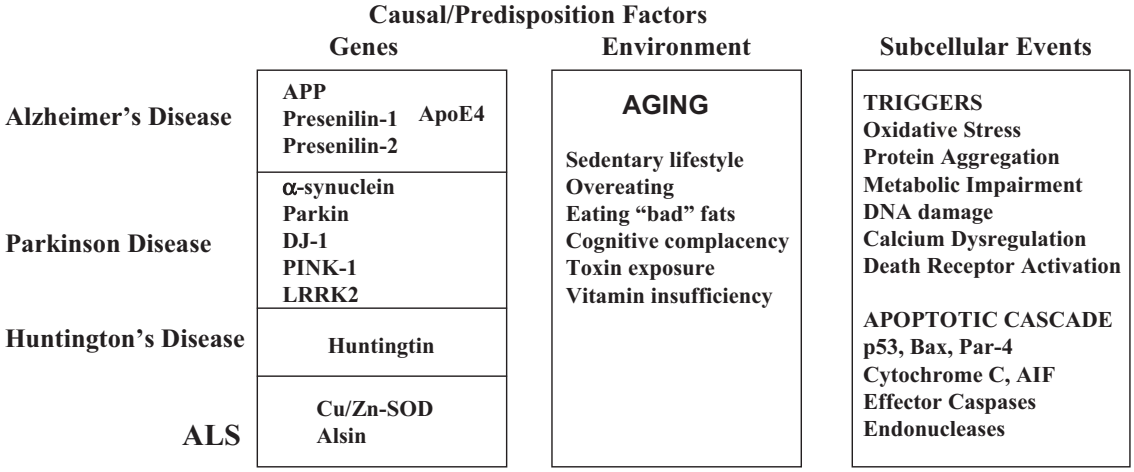

FIG. 3. Genetic and environmental factors may cause, or increase the risk of, neurodegenerative disorders by rendering neurons vulnerable to apoptosis. A small percentage of cases of AD, PD, and ALS are caused by mutations in the indicated genes (apoE4 increases the risk of AD), whereas all cases of HD are caused by mutations in huntingtin. Aging is the major non-genetic factor that promotes neurodegenerative disorders, whereas environmental factors such as lack of exercise, overeating, a poor diet, and exposure to toxins may increase disease risk. The indicated alterations in neurons that occur as the result of genetic and environmental factors may trigger apoptosis (right).

rons does occur in each of these disorders. Levels of activated caspase-3 are increased in affected brain regions in AD (hippocampus and association cortices), PD (substantia nigra), HD (striatum), and ALS (spinal cord) compared with nonvulnerable regions in the same patients and/or with the same regions in neurologically normal subjects, and immunohistochemical analyses of tissue sections from patients using antibodies that selectively recognize activate caspase-3 or caspase cleavage products have demonstrated the presence of abnormally high amounts of this marker of apoptosis in the same populations of neurons that die in the disorder (51, 75, 114, 132, 137). Other markers of apoptosis are also associated with dying neurons in the different disorders. For example, levels of Bax and p53 are increased in the neurons affected in AD (30, 125), PD (131, 132), and ALS (76, 93). It has also been reported that levels of prostate apoptosis response-4 (Par-4), a proapoptotic protein that acts upstream of mitochondrial changes, is increased in degenerating neurons in the brains of AD patients (48). Conversely, Par-4 was not detected in vulnerable dopaminergic neurons in the substantia nigra of PD patients (92).

Data from animal and cell-culture models

Animal models of neurodegenerative disorders include those in which selective neuronal degeneration is induced by administration of neurotoxins, and those in which mutant genes that cause early-onset inherited disease in humans are expressed in transgenic mice. Although not accurately recapitulating the molecular pathology of the human disease, toxin-based animal models do involve selective damage to the same neuronal populations and behavioral symptoms similar to the disease. Examples include: kainic acid–induced damage to hippocampal and cholinergic neurons, resulting in learning and memory deficits (AD); 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)-6-hydroxydoamine–or rotenone-induced damage to substantia nigra dopaminergic neurons, resulting in motor dysfunction (PD); and 3-NP (3-nitropropionic acid)- or quinolinic acid–induced damage to striatal neurons, resulting in motor deficits (HD) (10, 11, 13, 134). Transgenic mouse models of AD have been developed in which single or multiple mutant genes are expressed including those encoding AD-linked mutations in the amyloid precursor protein (APP) and presenilin-1, and/or mutations in tau that cause frontotemporal lobe dementia in humans (32, 97). Genetic models relevant to PD include α-synuclein mutant mice (Fleming *et al*., 2005); HD is modeled in huntingtin mutant mice (116), and ALS, in Cu/Zn-SOD mutant mice (7). Cell-culture models involved exposing cultured neurons to conditions believed to occur in the disease *in vivo*. Examples include exposure to amyloid β-peptide (AD model), overexpression of mutant α-synuclein (PD) or huntingtin (HD), or glucose and oxygen deprivation (stroke; for example, hypoxia as a stroke model). In several cases, the animal models have proven useful in evaluating the role of apoptosis in the death of neurons.

Alzheimer's disease. Soon after the identification of Aβ as the pathogenic peptide in AD, it was shown that synthetic Aβ can induce apoptosis of cultured neurons (143). More recent studies have provided evidence that Aβ kills neurons by first inducing membrane-associated oxidative stress, resulting in lipid peroxidation and the production of 4-hydroxynonenal and ceramide, which activate the intrinsic mitochondria-dependent apoptosis pathway (29, 64, 85). Several lines of APP mutant transgenic mice develop age-dependent accumulation of Aβ in the hippocampus and cerebral cortex, but in most cases, no evidence exists for degeneration and death of neurons in such mice. However, gene-expression analyses have provided evidence that genes involved in apoptosis are upregu-

lated relatively early in the brains of APP mutant mice, before the appearance of Aβ plaques (111). In addition, transgenic mice expressing an APP mutation that interferes with processing by α-secretase exhibited extensive neurodegeneration and apoptosis in the hippocampus and cerebral cortex (91). Recently, a novel triple-mutant AD mouse model was produced in which the mice express mutant presenilin-1, APP, and tau (97). The latter mice develop age-dependent Aβ and tau pathology and dendritic atrophy (97; and M. Mattson and R. Mervis, unpublished data). Whether apoptosis occurs in neurons in the latter model remains to be established.

It has been reported that neurons in the brains of APP mutant transgenic mice are more vulnerable to death induced by several different means. For example, when APP mutant mice are maintained on a diet that elevates homocysteine levels, hippocampal pyramidal neurons associated with Aβ deposits degenerate (66). In another study, prolonged infusion of an antibody against transthyretin into the hippocampus of mice overexpressing mutant APP resulted in increased Aβ levels, tau phosphorylation, and apoptosis of CA1 hippocampal neurons (124). Aβ may induce apoptosis by downregulating Bcl-2 and upregulating Bax (101) and by inducing oxidative stress and apoptotic cascades in synapses and dendrites (44, 79, 128). Presenilin-1 mutant mice exhibit no overt phenotypes, but studies have shown that neurons from such mice are more vulnerable to excitotoxicity and apoptosis (20, 47, 50). Cell-culture studies have provided evidence that mutant presenilin-1 perturbs ER calcium homeostasis, resulting in enhanced calcium release, which sensitizes neurons to apoptosis induced by trophic factor deprivation and oxidative stress (47). Antiapoptotic neurotrophic factors such as IGF-1 can protect neurons against the cell death–promoting effects of Aβ and mutations in presenilin-1 (49, 96).

Parkinson disease. Evidence for apoptosis has been obtained in analyses of brains of mice and rats administered the neurotoxins MPTP and 6-hydroxydopamine. For example, levels of Bax are increased in dopaminergic neurons in the substantia nigra in mice after administration of MPTP (52). Levels of Par-4 are increased in dopaminergic neurons of MPTP-treated mice and monkeys, and downregulation of Par-4 by using an antisense approach protected neurons against apoptosis (34). Dopaminergic neurons in transgenic mice overexpressing Bcl-2 (98), dominant-negative caspase-1 (62), or XIAP (25) exhibit resistance to MPTP-induced death, strongly suggesting that the neurons die by apoptosis in this model of PD. Dopaminergic neurons in Bax-deficient mice are also resistant to MPTP (136). Low-molecular-weight inhibitors of p53 were shown to be effective in protecting dopaminergic neurons and improving functional outcome in the MPTP mouse model of PD (35). Studies of the pathogenic actions of α-synuclein mutations (or increased gene dosage) also support a role for apoptosis in PD. For example, overexpression of mutant α-synuclein decreases proteasome activity and increases the sensitivity of cells to mitochondria-dependent apoptosis (129), and overexpression mutant or wild-type human α-synuclein induces apoptosis in dopaminergic neurons (148). Some data also suggest that mutant α-synuclein renders neurons vulnerable to toxin-induced apoptosis (127).

Huntington's disease. Examination of brain sections from HD patients and quinolinic acid–treated rats provided early evidence that neurons die by apoptosis in AD (109). However, activated caspase-9 and caspases-3 activities were observed only in severe neuropathologic grades in HD patients and HD mice, suggesting that apoptosis may play a greater role in neuronal death at end-stage disease (61). Studies in which mutant huntingtin is expressed in cultured neurons and transgenic mice have demonstrated that huntingtin is cleaved by proapoptotic cysteine proteases including caspases and apopain (24, 41, 45). Cleaved polyglutamine-containing aggregates of huntingtin accumulate in the nucleus and cytoplasm of neurons. Lymphoblasts from HD patients exhibit increased sensitivity to mitochondria-mediated apoptosis, which is exacerbated with increasing polyglutamine repeat length (118). Wang *et al*. (140) provided evidence that neurons may undergo either mitochondrial caspase-independent (apoptosis-inducing factor) or caspase-dependent (Smac/ Diablo and cytochrome *c*) apoptosis in HD. In addition, they found that minocycline can inhibit both caspase-independent and -dependent mitochondrial cell death pathways in huntingtin mutant mice. Studies of huntingtin mutant mice suggest that p53 plays a key role in apoptosis of striatal and cortical neurons upstream of mitochondrial changes (5). Mutant huntingtin may also promote apoptosis by inhibiting CREB-mediated production of BDNF (69). Other studies have provided evidence that the transcription factor NF-κB protects striatal neurons against apoptosis induced by the mitochondrial toxin 3-NP (145). Mutant huntingtin has also been shown to perturb cellular calcium homeostasis, which may play a role in apoptosis of striatal medium spiny neurons in HD (130).

Amyotrophic lateral sclerosis. Levels of Bax and p53 are increased in spinal cord motor neurons of ALS patients compared with age-matched control subjects (76, 93). In addition, caspase-9 activity was increased in spinal cord tissue of ALS patients, indicating activation of the mitochondrial apoptosis pathway in this disease (56). Studies of cultured primary motor neurons and motor neuron–like cell lines expressing ALS-linked copper/zinc superoxide dismutase (Cu/Zn-SOD) mutations have provided evidence that motor neurons undergo apoptosis in familial ALS. For example, levels of activated caspase-1 are increased in association with degeneration of motor neurons in Cu/Zn-SOD mutant mice (102). Infusion of the broad-spectrum caspase inhibitor zVAD-fmk into the cerebrospinal fluid of Cu/Zn-SOD mutant mice resulted in a decreased in caspase-1 and caspase-3 activities, and delayed disease onset and mortality, providing direct evidence that apoptosis plays a major role in this model of ALS (71). Overexpression of Bcl-2 protects motor neurons against the pathogenic effect of mutant Cu/Zn-SOD resulting in an extension of survival in the mice (138). Overexpression of the natural caspase-9 inhibitor XIAP attenuated disease progression without delaying onset in Cu/Zn-SOD mutant mice (56). Mutant Cu/Zn-SOD may promote apoptosis by sequestering antiapoptotic proteins that act upstream of caspase activation including Bcl-2 and heat-shock proteins (99, 103).

Motor neurons in ALS may have increased oxidative stress resulting in membrane lipid peroxidation and activation of

sphingomyelinases. The lipid peroxidation product 4-hydroxynonenal, and ceramides liberated from sphingomyelin by sphingomyelinases, can induce neuronal apoptosis and are implicated in the pathogenesis of ALS (28, 105). Apolipoprotein E2/3 may protect neurons against oxidative stress by binding 4-hydroxynonenal (106). Further evidence for a role for oxidative stress in the death of neurons in ALS comes from studies showing that nitric oxide can displace zinc from Cu/Zn-SOD resulting in increased cytotoxicity of the enzyme (37). Oxidative stress may contribute to dysregulation of cellular calcium homeostasis, which can increase the vulnerability of motor neurons to excitotoxic apoptosis (65). Finally, autoantibodies against motor neuron antigens have been found circulating in ALS patients, and exposure of cultured motor neurons to such immunoglobulins can trigger apoptosis, suggesting a role for immune attack on motor neurons in the pathogenesis of ALS (1).

IMPLICATIONS FOR THE PREVENTION AND TREATMENT OF NEURODEGENERATIVE DISORDERS

The need for treatments for neurodegenerative disorders is profound as the numbers of those affected with AD and PD continue to increase. Currently only treatments that have been shown to be (modestly) effective in slowing disease are agents that protect neurons against excitotoxic apoptosis: memantine for AD (17) and riluzole for ALS (89). The kinds of findings described earlier provide evidence that apoptosis of neurons does occur in several neurodegenerative disorders. The potential of and caveats for treatments that target apoptosis in neurodegenerative disorders have been reviewed elsewhere (135, 139). Experiments in which pharmacologic agents and dietary or other environmental manipulations protected neurons against apoptosis and improved functional outcome in animal models studies suggest a potential beneficial effect of such approaches in preventing and treating human neurodegenerative disease. The most effective means of preventing apoptosis and preserving neuronal function is to abolish the triggering event. For example, agents that prevent the production of Aβ for the treatment of AD, eliminating exposure to neurotoxins that may cause PD, or preventing the expression of mutant huntingtin as a treatment for HD. Once the initiating events in the neurodegenerative process have been triggered, specific early events in the apoptotic cascade can be targeted. Examples include antioxidants or agents that enhance the production of endogenous antioxidants to block apoptosis at a premitochondrial step (26, 108, 141), agents such as creatine that stabilize cellular energy levels (38, 63), and agents that block DNA damage–response pathways, such as poly-ADP-ribose polymerase (PARP) and p53 inhibitors (35, 74). Targets farther downstream of the triggering events have also been successfully blocked to prevent apoptosis. Among such agents are cyclosporine, which blocks mitochondrial membrane permeability transition pores, dantrolene, which blocks ER calcium channels, and caspase inhibitors. An alternative (or complementary) strategy for preventing apoptosis is to activate antiapoptotic pathways. This might be accomplished by administering a growth factor (bFGF, BDNF, GDNF, *etc*.) that activates a signaling pathway that induces the expression of Bcl-2, antioxidant enzymes, or IAPs, for example. Antiapoptotic pathways can also be activated by regular exercise, dietary restriction, and cognitive stimulation (86).

Despite the reported effectiveness of numerous pharmacologic agents in animal models of AD, PD, HD, and ALS, when tested in human patients, the same agents are usually found not to have a significant effect on the course of the disease (119). Many possible explanations exist for negative results in human trials, including differences in the underlying cellular and molecular mechanisms in animal models and the corresponding human disease, greater heterogeneity in the disease process among human patients compared with inbred rodents, and dosing and length of treatment. Importantly, in most animal models, drug administration is initiated before the onset of the disease, whereas in human studies, the drug is given after disease onset. Therefore, the numerous positive results reported in animal models were in studies in which what was tested was the ability of the drug to prevent or delay disease onset. It is therefore, in my opinion, of major importance to identify and implement preventive approaches for apoptotic neurodegenerative disorders. In this regard, studies of animal models and human populations suggest that, indeed, prevention is possible. Housing animals in an enriched environment (68, 120) or maintaining them on dietary-restriction regimens (intermittent fasting and/or caloric restriction (36, 77, 104) retards the disease process and improves functional outcomes in models of AD, PD, and HD. In the HD and PD models, dietary restriction increased the resistance of neurons in the affected brain regions to apoptosis. Epidemiologic findings in human studies suggest that the risk of late-onset AD and PD can be decreased by regular exercise and low-energy diets in adult life (88).

ABBREVIATIONS

Aβ, amyloid beta-peptide; AD, Alzheimer's disease; AIF, apoptosis-inducing factor; ALS, amyotrophic lateral sclerosis; APP, amyloid precursor protein; BDNF, brain-derived neurotrophic factor; CREB, cyclic AMP response element–binding protein; Cu/Zn-SOD, copper/zinc superoxide dismutase; bFGF, basic fibroblast growth factor; ER, endoplasmic reticulum; GDNF, glial cell line–derived neurotrophic factor; HD, Huntington disease; HSP, heat-shock protein; IAP, inhibitor of apoptosis protein; IGF-1, insulin-like growth factor-1; MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; NGF, nerve growth factor; PARP, poly-ADP-ribose polymerase; 3-NP, 3-nitropropionic acid; PD, Parkinson disease; PTP, permeability transition pore.

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