Huntington's disease, in which using low-dose memantine to selectively block the extrasynaptic receptors is beneficial.

Although excitotoxicity is clearly implicated in the pathogenesis of cell death in stroke, to date treatment with NMDA antagonists has not proven to be clinically useful. One approach has been to use an inhibitor of the postsynaptic density-95 protein that uncouples NMDA receptors from neurotoxic pathways, including the generation of nitric oxide. This approach was effective in a primate stroke model and in a phase 2 clinical trial of stroke associated with endovascular repair of cerebral aneurysms. Transient receptor potentials (TRPs) are calcium channels that are activated by oxidative stress in parallel with excitotoxic signal pathways. In addition, glutamate-independent pathways of calcium influx via acid-sensing ion channels have been identified. These channels transport calcium in the setting of acidosis and substrate depletion, and pharmacologic blockade of these channels markedly attenuates stroke injury. These channels offer a potential new therapeutic target for stroke.

Apoptosis, or programmed cell death, plays an important role in both physiologic and pathologic conditions. During embryogenesis, apoptotic pathways operate to destroy neurons that fail to differentiate appropriately or reach their intended targets. There is mounting evidence for an increased rate of apoptotic cell death in a variety of acute and chronic neurologic diseases. Apoptosis is characterized by neuronal shrinkage, chromatin condensation, and DNA fragmentation, whereas necrotic cell death is associated with cytoplasmic and mitochondrial swelling followed by dissolution of the cell membrane. Apoptotic and necrotic cell death can coexist or be sequential events, depending on the severity of the initiating insult. Cellular energy reserves appear to have an important role in these two forms of cell death, with apoptosis favored under conditions in which ATP levels are preserved. Evidence of DNA fragmentation has been found in a number of degenerative neurologic disorders, including AD, Huntington's disease, and ALS. The best characterized genetic neurologic disorder related to apoptosis is infantile spinal muscular atrophy (Werdnig-Hoffmann disease), in which two genes thought to be involved in the apoptosis pathways are causative.

Mitochondria are essential in controlling specific apoptosis pathways. The redistribution of cytochrome c, as well as apoptosis-inducing factor (AIF), from mitochondria during apoptosis leads to the activation of a cascade of intracellular proteases known as *caspases*. Caspase-independent apoptosis occurs after DNA damage, activation of poly-ADP-ribose polymerase, and translocation of AIF into the nucleus. Redistribution of cytochrome c is prevented by overproduction of the apoptotic protein BCL2 and is promoted by the proapoptotic protein BAX. These pathways may be triggered by activation of a large pore in the mitochondrial inner membrane known as the *permeability transition pore*, although in other circumstances, they occur independently. The permeability transition pore is made up of dimers of ATP synthase and is activated by cyclophilin D, leading to large calcium fluxes across the inner mitochondrial membrane. Certain forms of congenital muscular dystrophies are caused by mutations in collagen VI, which leads to increased activation of the permeability transition pore. Recent studies suggest that blocking the mitochondrial pore reduces both hypoglycemic and ischemic cell death. Mice deficient in cyclophilin D, a key protein involved in opening the permeability transition pore, are resistant to necrosis produced by focal cerebral ischemia.

PROTEIN AGGREGATION AND NEURODEGENERATION

The possibility that protein aggregation plays a role in the pathogenesis of neurodegenerative diseases is a major focus of current research. Protein aggregation is a major histopathologic hallmark of neurodegenerative diseases. Deposition of β-amyloid is strongly implicated in the pathogenesis of AD. Genetic mutations in familial AD cause increased production of β-amyloid with 42 amino acids, which has an increased propensity to aggregate, as compared to β-amyloid with 40 amino acids. Furthermore, mutations in the amyloid precursor protein (APP), which reduce the production of β-amyloid, protect against the development of AD and are associated with preserved cognition in the elderly. Mutations in genes encoding the MAPT lead to altered splicing of tau and the production of neurofibrillary tangles in frontotemporal dementia and progressive supranuclear palsy. Familial Parkinson's disease is associated with mutations in *leucine-rich repeat kinase 2 (LRRK2), α-synuclein, parkin, PINK1,* and *DJ-1*. PINK1 is a mitochondrial kinase (see below), and DJ-1 is a protein involved in protection from oxidative stress. Parkin, which causes autosomal recessive early-onset Parkinson's disease, is a ubiquitin ligase. The characteristic histopathologic feature of Parkinson's disease is the Lewy body, an eosinophilic cytoplasmic inclusion that contains both neurofilaments and α-synuclein. Huntington's disease and cerebellar degenerations are associated with expansions of polyglutamine repeats in proteins, which aggregate to produce neuronal intranuclear inclusions. Familial ALS is associated with superoxide dismutase mutations and cytoplasmic inclusions containing superoxide dismutase. An important finding was the discovery that ubiquinated inclusions observed in most cases of ALS and the most common form of frontotemporal dementia are composed of TAR DNA binding protein 43 (TDP-43). Subsequently, mutations in the TDP-43 gene, and in the fused in sarcoma gene (FUS), were found in familial ALS. Both of these proteins are involved in transcription regulation as well as RNA metabolism. In autosomal dominant neurohypophyseal diabetes insipidus, mutations in vasopressin result in abnormal protein processing, accumulation in the endoplasmic reticulum, and cell death.

Another key mechanism linked to cell death is mitochondrial dynamics, which refers to the processes involved in movement of mitochondria, as well as in mitochondrial fission and fusion, which play a critical role mitochondrial turnover and in replenishment of damaged mitochondria. Mitochondrial dysfunction is strongly linked to the pathogenesis of a number of neurodegenerative diseases such as Friedreich's ataxia, which is caused by mutations in an iron-binding protein that plays an important role in transferring iron to iron-sulfur clusters in aconitase and complex I and II of the electron transport chain. Mitochondrial fission is dependent on the dynamin-related proteins (Drp1), which bind to its receptor Fis, whereas mitofuscins 1 and 2 (MF 1/2) and optic atrophy protein 1 (OPA1) are responsible for fusion of the outer and inner mitochondrial membrane, respectively. Mutations in MFN2 cause Charcot-Marie-Tooth neuropathy type 2A, and mutations in OPA1 cause autosomal dominant optic atrophy. Both β-amyloid and mutant huntingtin protein induce mitochondrial fragmentation and neuronal cell death associated with increased activity of Drp1. In addition, mutations in genes causing autosomal recessive Parkinson's disease, *parkin* and *PINK1*, cause abnormal mitochondrial morphology and result in impairment of the ability of the cell to remove damaged mitochondria by autophagy.

One major scientific question is whether protein aggregates directly contribute to neuronal death or whether they are merely secondary bystanders. A current focus in all the neurodegenerative diseases is on small protein aggregates termed *oligomers*. These may be the toxic species of β-amyloid, α-synuclein, and proteins with expanded polyglutamines such as are associated with Huntington's disease. Protein aggregates are usually ubiquinated, which targets them for degradation by the 26S component of the proteasome. An inability to degrade protein aggregates could lead to cellular dysfunction, impaired axonal transport, and cell death by apoptotic mechanisms.

Autophagy is the degradation of cystolic components in lysosomes. There is increasing evidence that autophagy plays an important role in degradation of protein aggregates in the neurodegenerative diseases, and it is impaired in AD, Parkinson's disease, and Huntington's disease. Autophagy is particularly important to the health of neurons, and failure of autophagy contributes to cell death. In Huntington's disease, a failure of cargo recognition occurs, contributing to protein aggregates and cell death. Rapamycin, which induces autophagy, exerts beneficial therapeutic effects in transgenic mouse models of AD, Parkinson's disease, and Huntington's disease.

There is other evidence for lysosomal dysfunction and impaired autophagy in Parkinson's disease. Mutations in glucocerebrosidase are associated with 5% of all Parkinson's disease cases as well as 8–9% of patients with dementia with Lewy bodies. Therefore, this is the most