NS/202: Unit 4
Apoptosis and Necrosis

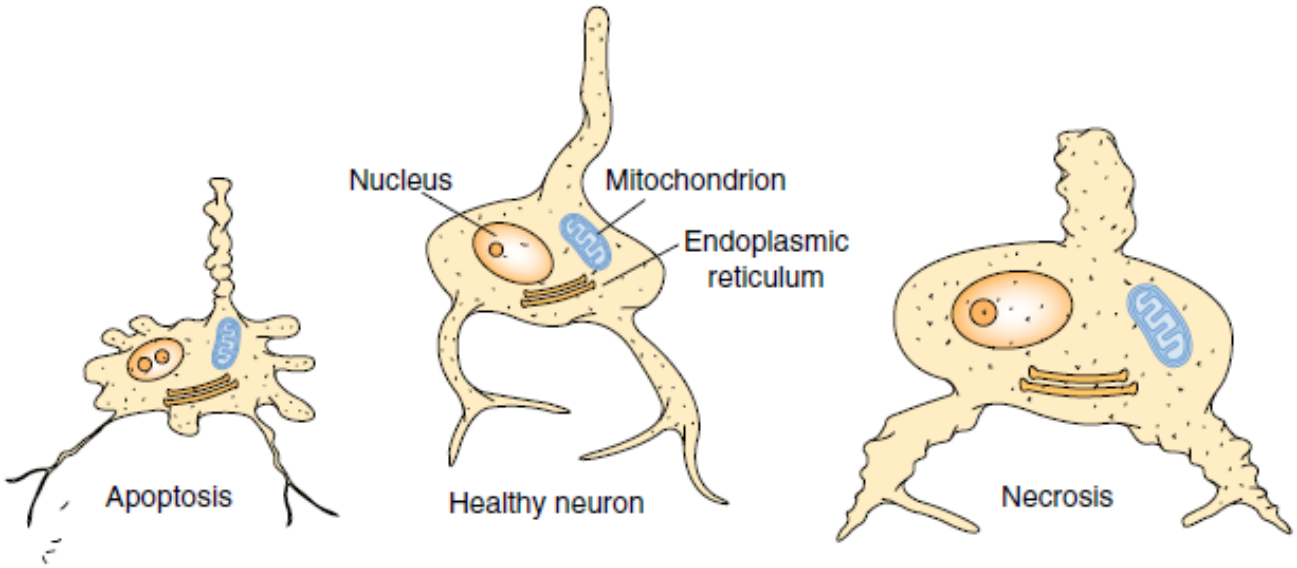
DISTINGUISHING FEATURES OF APOPTOSIS AND NECROSIS

- **During embryonic and postnatal development, and throughout adult life, many cells in the nervous system die**

- **Many of the morphological and biochemical changes that occur in cells that die by necrosis are very different from those that occur in apoptosis**

TABLE 35-1 Examples of caspase substrates

Cytoskeletal and associated proteins	Actin, spectrin, tau, vimentin, β-catenin, gelsolin, kinectin
Nuclear and DNA-associated proteins	Ataxia telangiectasia mutated (ATM), poly(ADP ribose) polymerase (PARP), DNA-dependent protein kinase, DNA replication factor C, DNA topoisomerase I, DNA fragmentation factor (DFF)45, inhibitor of caspase-activated DNAse (ICAD), lamins A, B1, and C
Signal transduction proteins	TRAF-1, Raf1, Ras, GAP, GDP dissociation inhibitor of Rho family GTPases, phospholipase A_2, Stat1
Kinases and phosphatases	Protein kinase Cd, Akt kinase, calcium/calmodulin-dependent protein kinase IV, mitogen-activated protein kinase kinase (MEKK-1), focal adhesion kinase (FAK), protein phosphatase (PP)2A, calcineurin
Transcription factors	NF-κB subunits p65 and p50, AP-2α, forkhead transcription factor FOXO3a, Max
Ion channels	IP3R1 and IP3R2, glutamate (AMPA) receptor subunits GluR1 and GluR4
Neurological-disorder-related proteins	Amyloid precursor protein (APP), presenilin-1, presenilin-2, parkin, tau, huntingtin, ataxin-3



Apoptosis	Necrosis
Cell shrinkage	Cell swelling
Maintenance of organellar integrity	Organellar swelling and damage
Maintenance of ATP levels	Depletion of ATP
Maintenance of ion homeostasis	Loss of ion homeostasis
Membrane surface blebbing	Membrane rupture
Nuclear chromatin condensation/fragmentation	Nuclear lysis
Requires synthesis of death effector proteins	Cessation of protein synthesis
Prevented by blocking steps in the death cascade	Irreversible
Does not adversely affect neighbor cells	Promotes death of neighbor cells

FIGURE 35-1 Distinguishing features of apoptosis and necrosis.

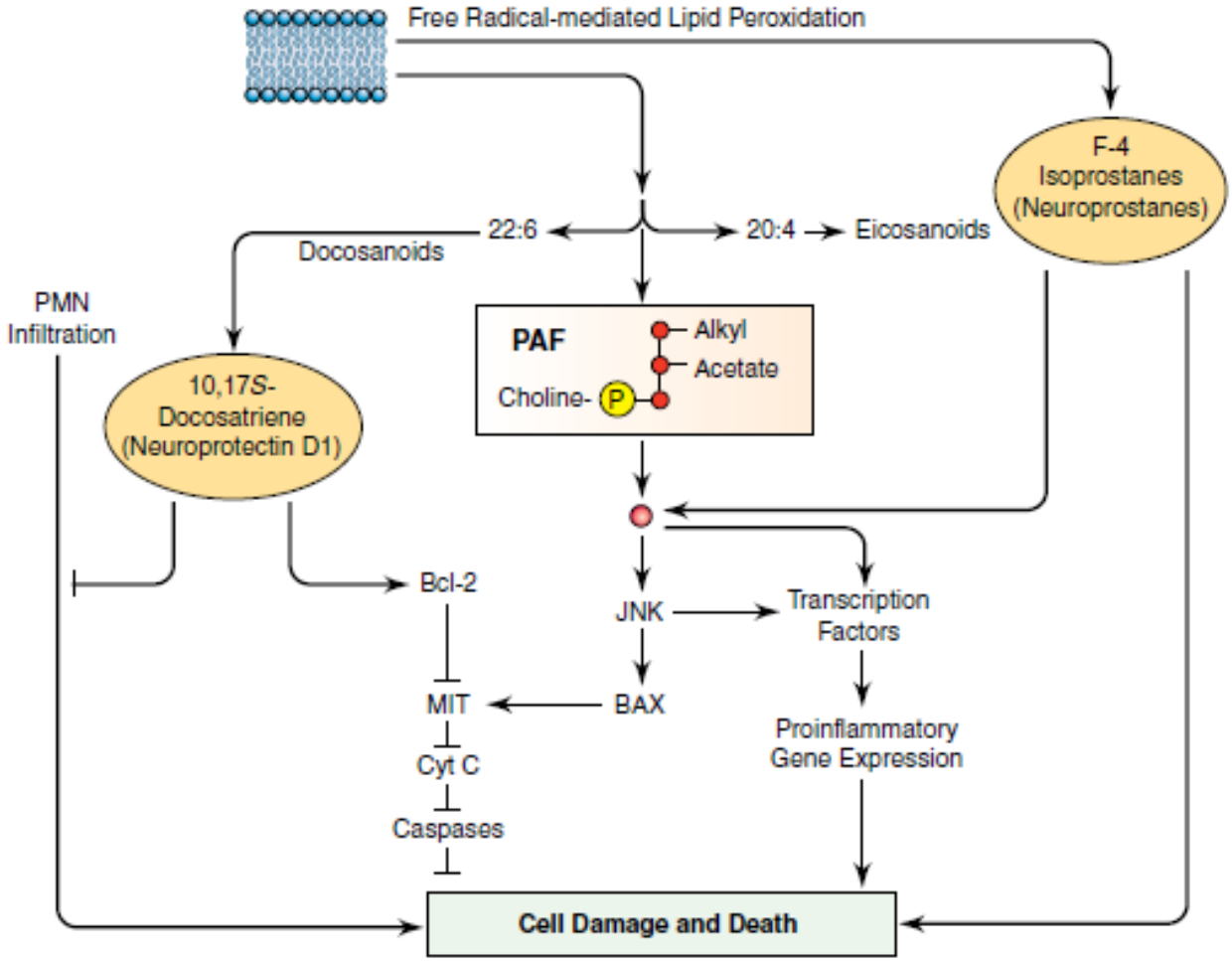


FIGURE 35-2 Phospholipids of cellular membranes can be peroxidized by free-radical-catalyzed reactions. Excessive accumulation of lipid peroxides contributes to cell damage and death. In the nervous system, these phospholipids contain the largest quantities of docosahexaenoic acid (22:6), which was recently demonstrated to be the precursor of the neuroprotective docosanoid 10,17*S*-docosatriene (neuroprotectin D1, NPD1). NPD1 counteracts proinflammatory cellular signaling and decreases polymorphonuclear leukocyte (PMN) infiltration in ischemic brain [16], and inactivates proapoptotic signaling and upregulates antiapoptotic signaling in oxidatively stressed retinal pigment epithelial cells [17].

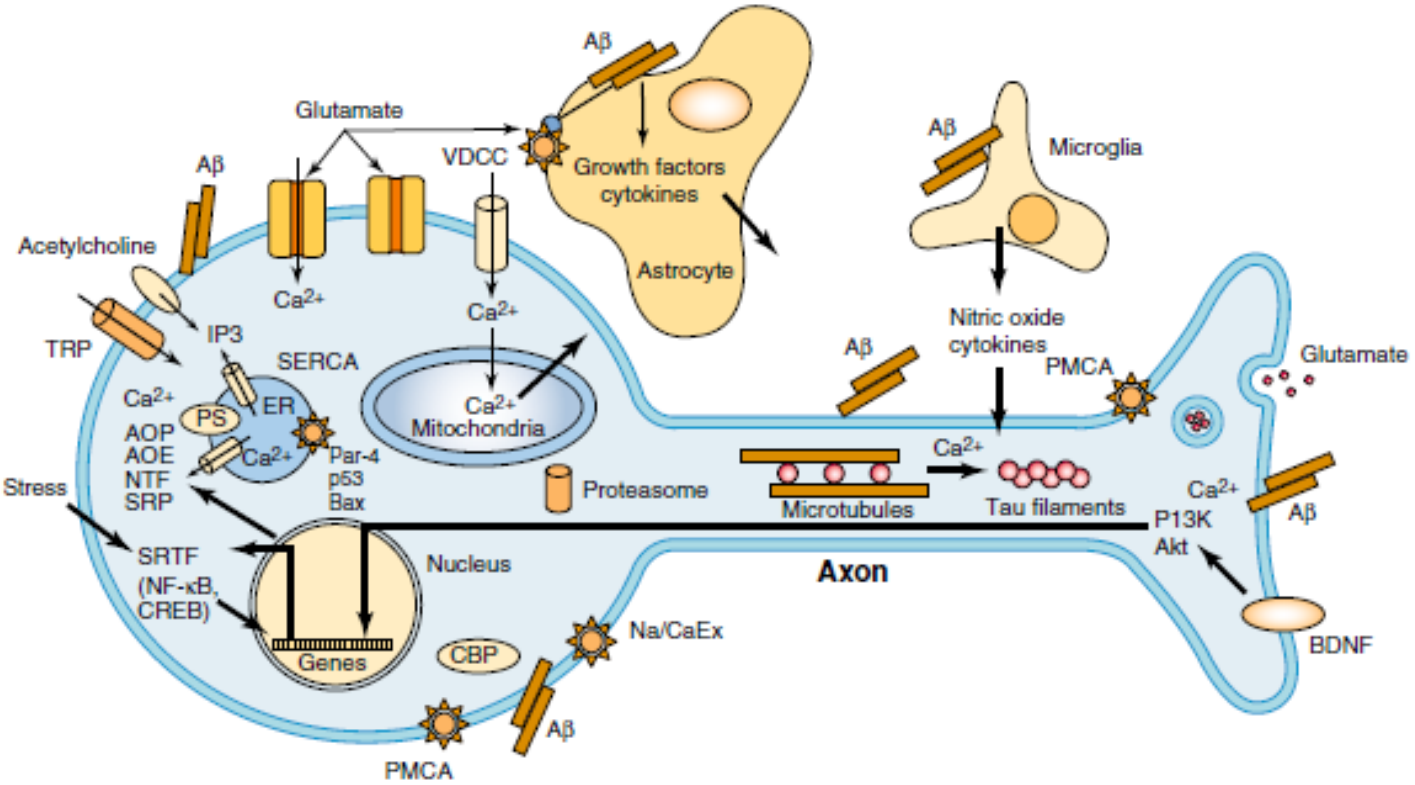


FIGURE 35-3 Examples of inter- and intracellular signaling mechanisms and biochemical cascades that can determine whether a neuron lives or dies in physiological and pathological settings. Neurons respond to a wide array of extracellular signals that can either prevent or promote cell death; examples include neuroprotective growth factors and neurotoxic amyloid β-peptide (*Aβ*). The calcium ion (Ca^{2+}) often plays important roles in determining whether neurons live or die. Excessive influx of Ca^{2+} through glutamate receptor channels, voltage-dependent Ca^{2+} channels and capacitative Ca^{2+} entry channels (*TRP*) in the plasma membrane, and/or excessive release of Ca^{2+} from endoplasmic reticulum (*ER*) and mitochondrial stores, can trigger apoptosis. On the other hand, effective removal of Ca^{2+} from the cytoplasm via the activities of plasma membrane (*PMCA*) and ER (*SERCA*) Ca^{2+}-ATPases, the plasma membrane Na^{+}/Ca^{2+} exchanger (*Na/CaEx*) or sequestration by Ca^{2+}-binding proteins (*CBP*) can prevent apoptosis. Cell death may also be triggered by oxidative stress, insufficient trophic factor support and abnormalities in the cytoskeleton, such as occur, for example, in Alzheimer's disease where microtubules depolymerize and the microtubule-associated protein tau forms abnormal aggregates. By activating transcription factors that induce the expression of cytoprotective genes, some signaling pathways can prevent cell death. For example, stress-responsive transcription factors such as NF-κB and CREB induce the expression of antiapoptotic proteins (*AOP;* Bcl-2 and IAPs, for example), antioxidant enzymes (*AOE*), neurotrophic factors (*NTF*) and stress resistance proteins (*SRP;* HSP-70 and GRP-78, for example). Microglia may facilitate neuronal death by producing neurotoxic substances such as nitric oxide and proinflammatory cytokines.

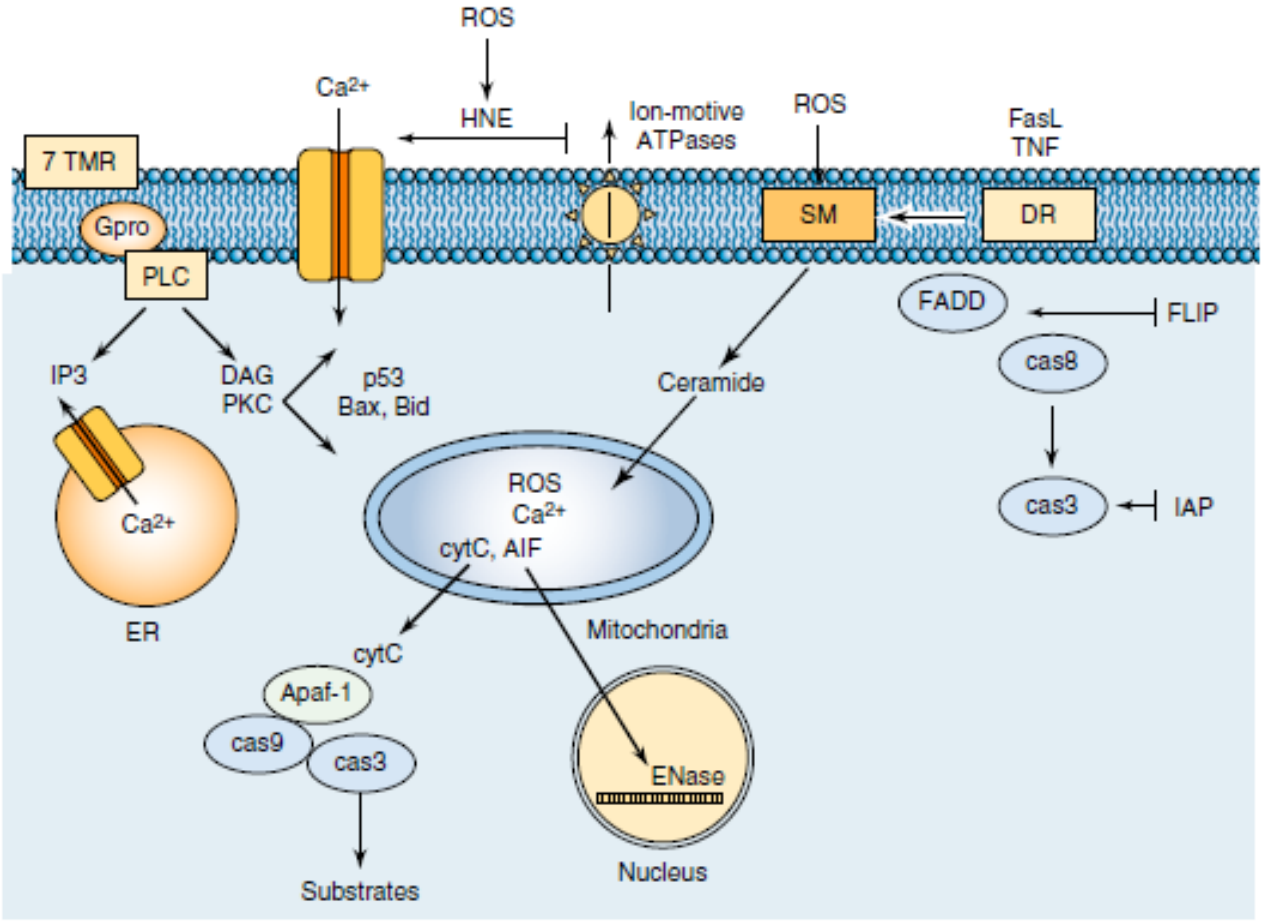


FIGURE 35-4 Examples of plasma-membrane-initiated cell death cascades. Many cells, including neurons, express so-called death receptors (*DR*). In the example shown, a receptor for Fas ligand (*FasL*) or tumor necrosis factor (*TNF*) binds a protein called FADD (Fas-associated death domain), which then 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 can also 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. Receptors with seven transmembrane domains (*7TMR*) coupled to 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*).

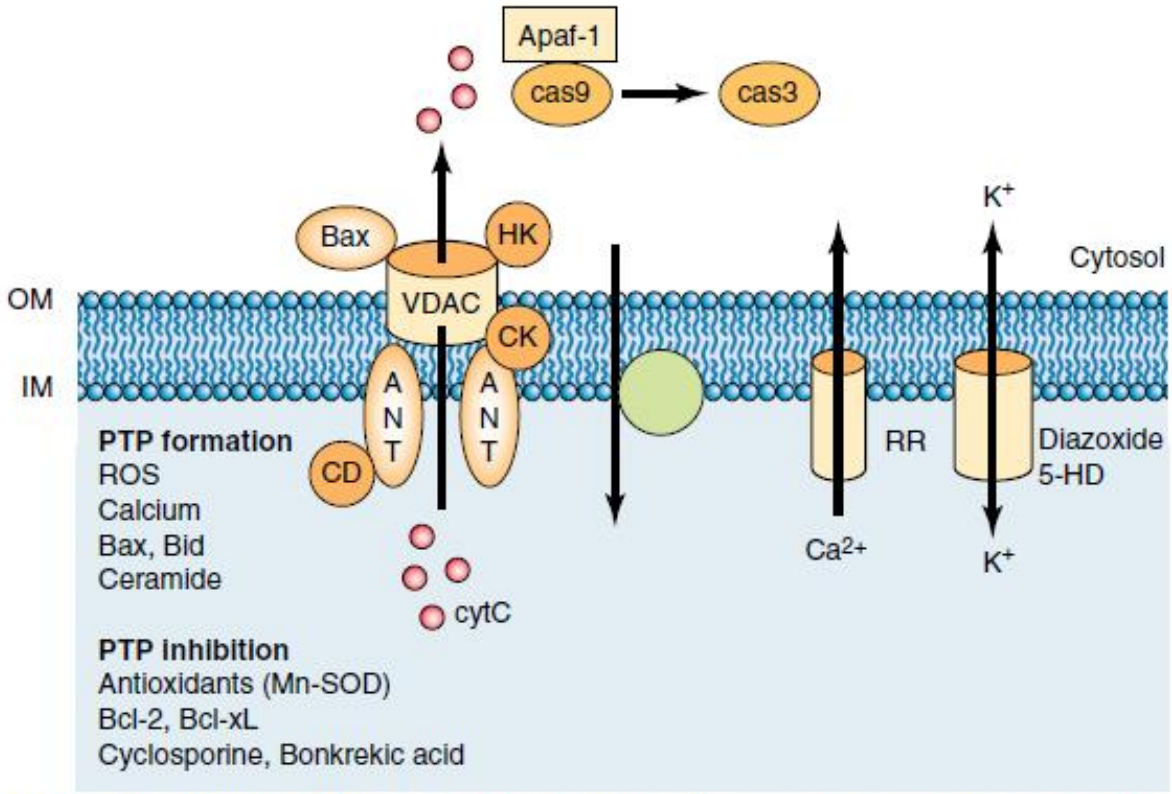


FIGURE 35-5 The presumptive mitochondrial permeability transition pore complex and its regulation by Ca^{2+} and K^+ fluxes. The membrane permeability transition pore is believed to consist of VDAC (voltage-dependent anion channel) and ANT (adenine nucleotide translocator) and associated proteins that modulate its opening including hexokinase (*HK*), creatine kinase (CK), cyclophilin D (*CD*) and Bax. Formation and opening of the channel results in the release of cytochrome C (*cytC*), which then binds to Apaf-1, resulting in the sequential activation of caspases 9 and 3. Mitochondrial membrane permeability pore formation is subject to regulation by fluxes of Ca^{2+} and K^+. Agents that suppress Ca^{2+} flux (*RR*, ruthenium red) and K^+ flux (*5-HD*, 5-hydroxydecanoate) can prevent pore formation. Interestingly, activation of mitochondrial K^+ channels with diazoxide can also prevent apoptosis by inducing a preconditioning response.

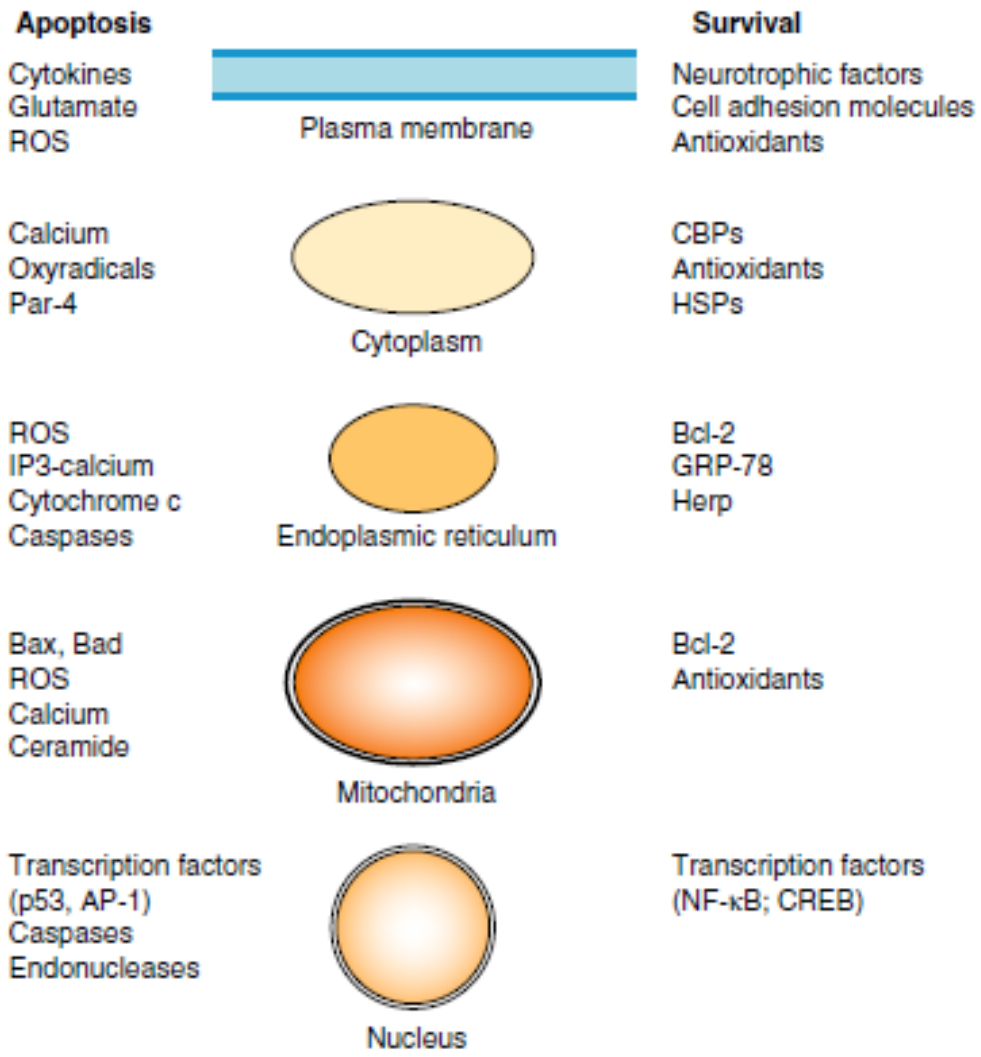


FIGURE 35-6 Examples of apoptotic and antiapoptotic mechanisms that act on or within different subcellular compartments. CBP, Ca^{2+} binding protein; CREB, cyclic AMP response element binding protein; HSP, heat shock protein; IP3, inositol 1,4,5-trisphosphate; ROS, reactive oxygen species.

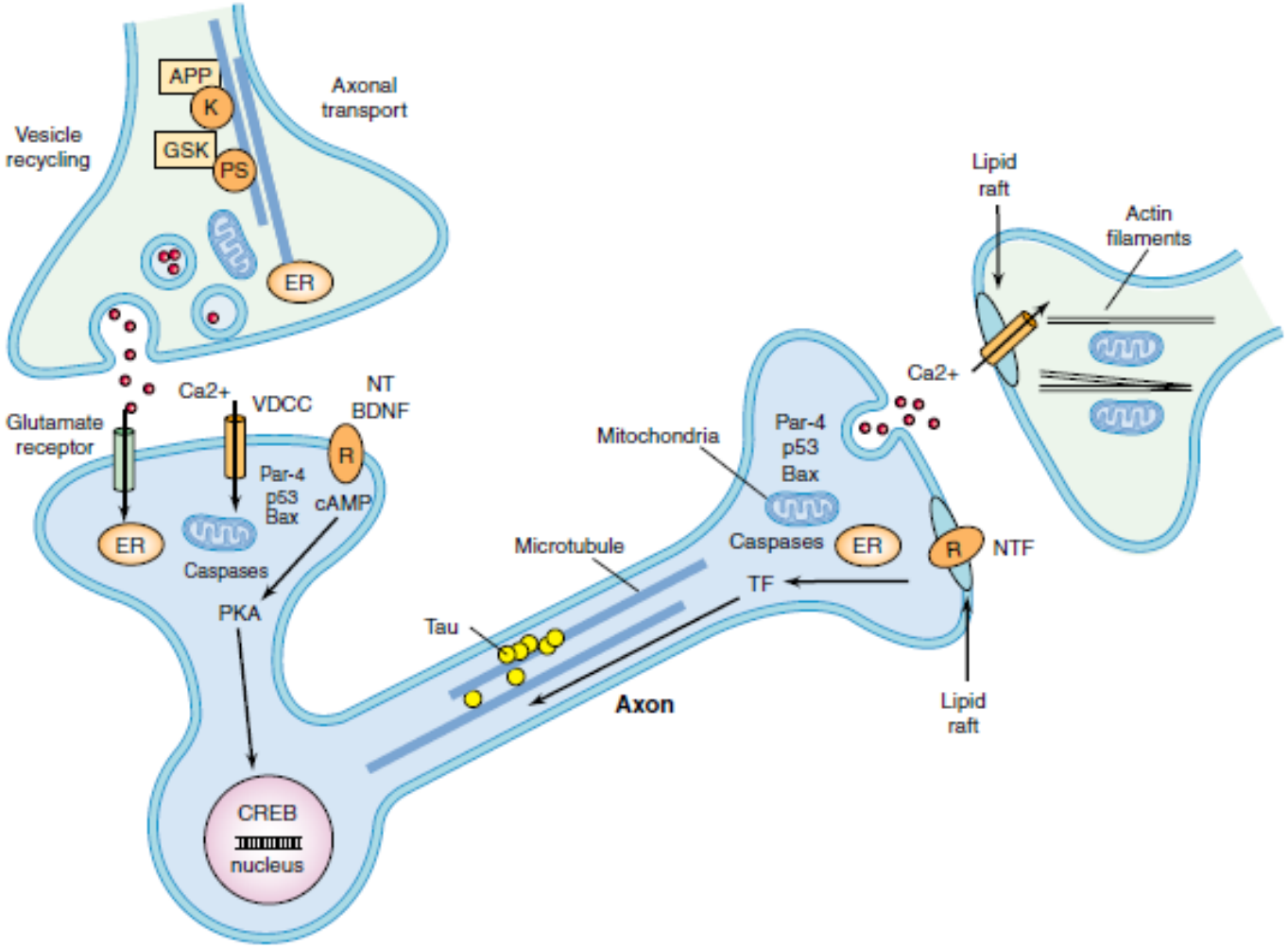


FIGURE 35-7 Apoptotic and anti-apoptotic synaptic signaling mechanisms. Synapses are sites where various signal transduction pathways are activated including those of neurotransmitters (*NT*; glutamate receptors linked to calcium influx and receptors coupled to cAMP production are shown), and neurotrophic factors (*NTF*). Synapses contain all the major organelles (except the nucleus) and proteins involved in apoptosis including *Bcl-2* family members, p53, Par-4, mitochondria and ER, and caspases. Alterations in axonal transport may also trigger apoptosis. *APP*, amyloid precursor protein; *CREB*, cyclic AMP response element binding protein; *ER*, endoplasmic reticulum; *GSK*, glycogen synthase kinase; *K*, kinesin; *PKA*, protein kinase A; *PS*, presenilin; *R*, receptor; *TF*, transcription factor; *VDCC*, voltage-dependent calcium channel.