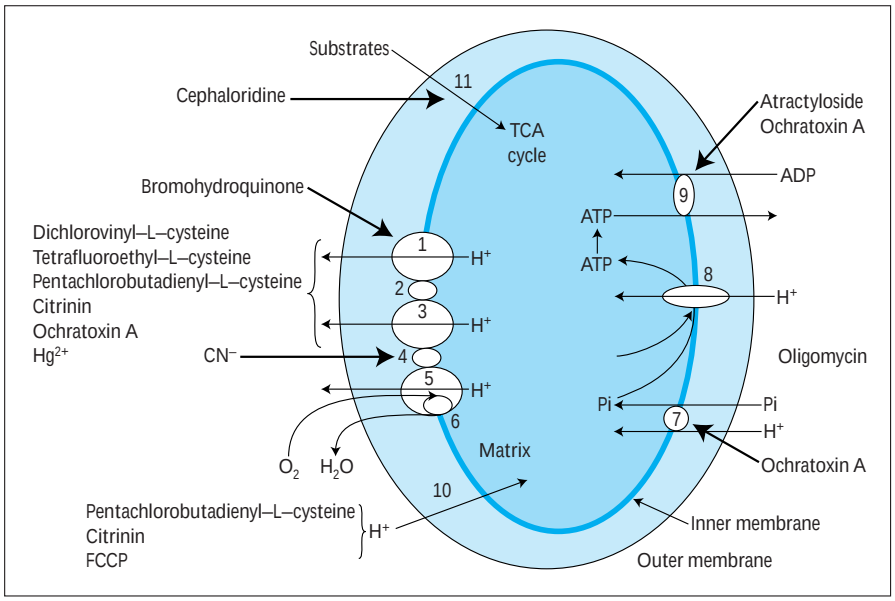

FIGURE 15-21

Some of the mitochondrial targets of nephrotoxicants: 1) nicotinamide adenine dinucleotide (NADH) dehydrogenase; 2) succinate dehydrogenase; 3) coenzyme Q–cytochrome C reductase; 4) cytochrome C; 5) cytochrome C oxidase; 6) cytochrome Aa_3; 7) H^+-Pi contransporter; 8) F_0F_1-ATPase; 9) adenine triphosphate/diphosphate (ATP/ADP) translocase; 10) protonophore (uncoupler); 11) substrate transporters.

Disruption of ion homeostasis

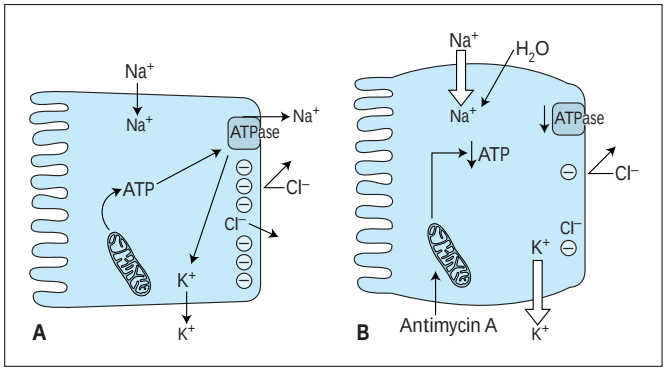

FIGURE 15-22

Early ion movements after mitochondrial dysfunction. **A**, A control renal proximal tubular cell. Within minutes of mitochondrial inhibition (*eg*, by antimycin A), ATP levels drop, resulting in inhibition of the Na^+, K^+-ATPase. **B**, Consequently, Na^+ influx, K^+ efflux, membrane depolarization, and a limited degree of cell swelling occur.

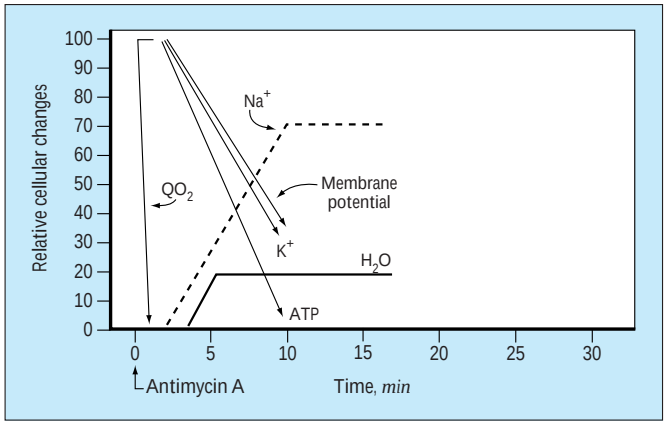

FIGURE 15-23

A graphic of the phenomena diagrammed in Figure 15-22.

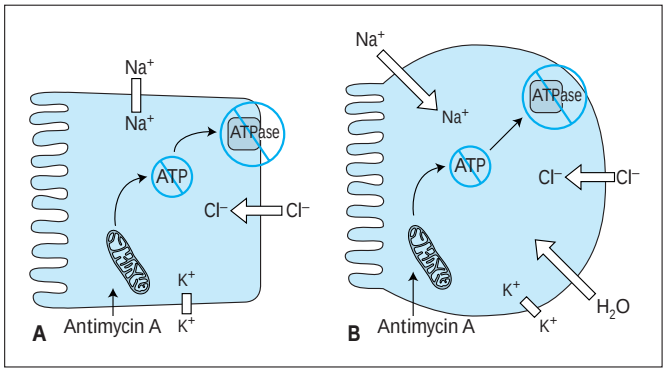

FIGURE 15-24

The late ion movements after mitochondrial dysfunction that leads to cell death/lysis. **A**, Cl^- influx occurs as a distinct step subsequent to Na^+ influx and K^+ efflux. **B**, Following Cl^- influx, additional Na^+ and water influx occur resulting in terminal cell swelling. Ultimately cell lysis occurs.

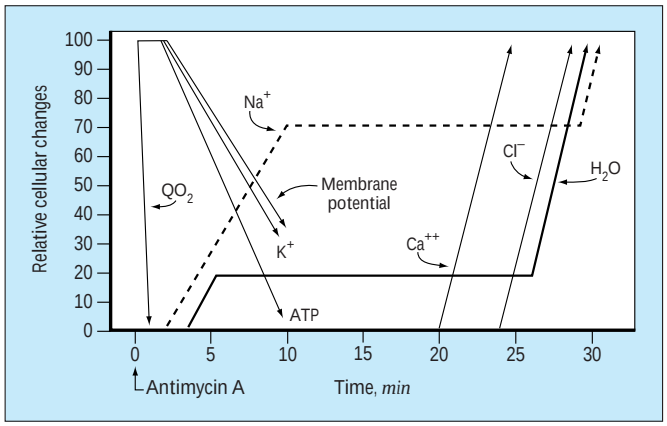

FIGURE 15-25
A graph of the phenomena depicted in Figures 15-22 through 15-24, illustrating the complete temporal sequence of events following mitochondrial dysfunction. QO_2—oxygen consumption.

Disregulation of regulatory enzymes

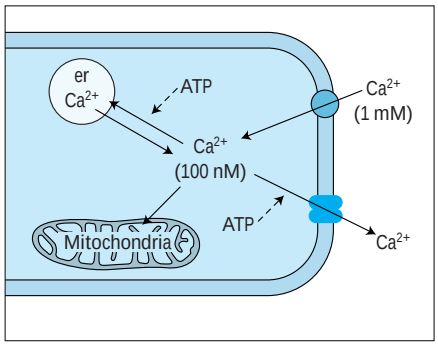

FIGURE 15-26
A simplified schematic drawing of the regulation of cytosolic free Ca^{2+}.

BIOCHEMICAL CHARACTERISTICS OF CALPAIN

Endopeptidase
Heterodimer: 80-kD catalytic subunit, 30-kD regulatory subunit
—Calpain and μ-calpain are ubiquitously distributed cytosolic isozymes
—Calpain and μ-calpain have identical regulatory subunits but distinctive catalytic subunits
—Calpain requires a higher concentration of Ca^{2+} for activation than μ-calpain
Phospholipids reduce the Ca^{2+} requirement
Substrates: cytoskeletal and membrane proteins and enzymes

FIGURE 15-27
Biochemical characteristics of calpain.

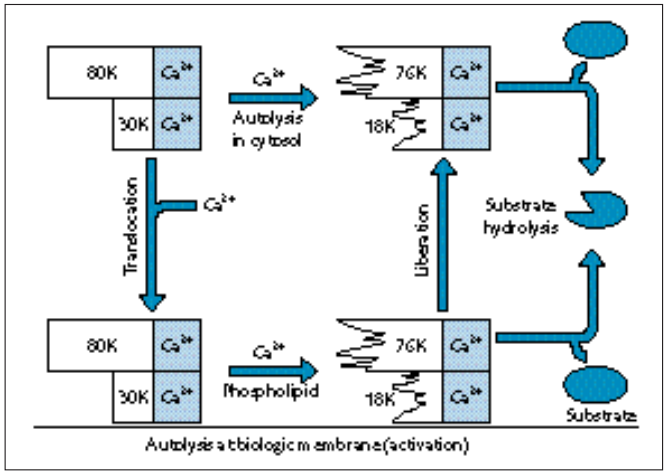

FIGURE 15-28
Calpain translocation. Proposed pathways of calpain activation and translocation. Both calpain subunits may undergo calcium (Ca^{2+})-mediated autolysis within the cytosol and hydrolyze cytosolic substrates. Calpains may also undergo Ca^{2+}-mediated translocation to the membrane, Ca^{2+}-mediated, phospholipid-facilitated autolysis and hydrolyze membrane-associated substrates. The autolyzed calpains may be released from the membrane and hydrolyze cytosolic substrates. (*From* Suzuki and Ohno [10], and Suzuki *et al.* [11]; with permission.)

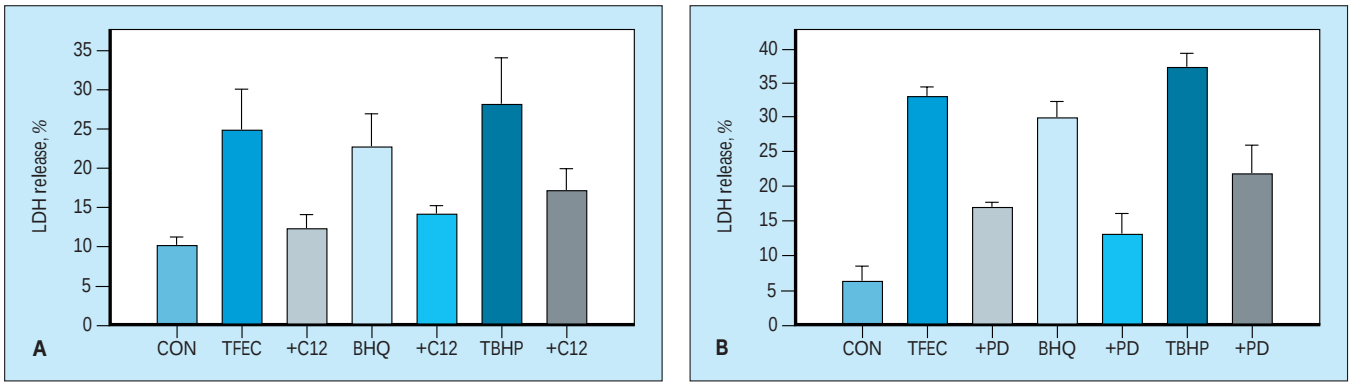

FIGURE 15-29

A, **B**, Dissimilar types of calpain inhibitors block renal proximal tubular toxicity of many agents. Renal proximal tubular suspensions were pretreated with the calpain inhibitor 2 (CI2) or PD150606 (PD). CI2 is an irreversible inhibitor of calpains that binds to the active site of the enzyme. PD150606 is a reversible inhibitor of calpains that binds to the calcium (Ca^{2+})-binding domain on the enzyme. The toxicants used were the haloalkane cysteine conjugate tetrafluoroethyl-L-cysteine (TFEC), the alkylating quinone bromohydroquinone (BHQ), and the model oxidant *t*-butylhydroperoxide (TBHP). The release of lactate dehydrogenase (LDH) was used as a marker of cell death. CON—control. (*From* Waters *et al*. [12]; with permission.)

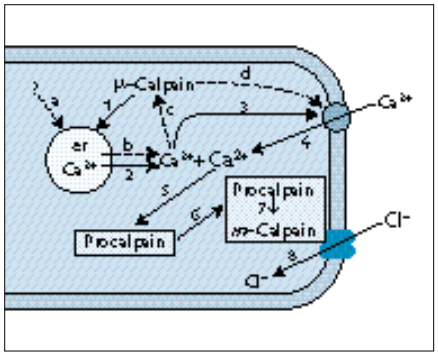

FIGURE 15-30

One potential pathway in which calcium (Ca^{2+}) and calpains play a role in renal proximal tubule cell death. These events are subsequent to mitochondrial inhibition and ATP depletion. 1) μ-Calpain releases endoplasmic reticulum (er) Ca^{2+} stores. 2) Release of er Ca^{2+} stores increases cytosolic free Ca^{2+} concentrations. 3) The increase in cytosolic free Ca^{2+} concentration mediates extracellular Ca^{2+} entry. (This may also occur as a direct result of er Ca^{2+} depletion.) 4) The influx of extracellular Ca^{2+} further increases cytosolic free Ca^{2+} concentrations. 5) This initiates the translocation of nonactivated *m*-calpain to the plasma membrane (6). 7) At the plasma membrane nonactivated *m*-calpain is autolyzed and hydrolyzes a membrane-associated substrate. 8) Either directly or indirectly, hydrolysis of the membrane-associated substrate results in influx of extracellular chloride ions (Cl^-). The influx of extracellular Cl^- triggers terminal cell swelling. *Steps a–d* represent an alternate pathway that results in extracellular Ca^{2+} entry. (*Data from* Waters *et al*. [12,13,14].)

PROPERTIES OF PHOSPHOLIPASE A_2 GROUP

Characteristics	Secretory	Cytosolic	Ca^{2+}-Independent	
Localization	Secreted	Cytosolic	Cytosolic	Membrane
Molecular mass	~14 kDa	~85 kDa	~40 kDa	unknown
Arachidonate preference	–	+	+	+
Ca^{2+} required	mM	(M	None	None
Ca^{2+} role	Catalysis	Memb. Assoc.	None	None

FIGURE 15-31

Biochemical characteristics of several identified phospholipase A_2s.