

FIGURE 14-20

Proposed role of nitric oxide (NO) in radiocontrast-induced acute renal failure (ARF). **A**, Administration of iohalamate, a radiocontrast dye, to rats increases medullary blood flow. Inhibitors of either prostaglandin production (such as the NSAID, indomethacin) or inhibitors of NO synthesis (such as L-NAME) abolish the compensatory increase in medullary blood flow that occurs in response to radiocontrast administration. Thus, the stimulation of prostaglandin and NO production after radiocontrast administration is important in maintaining medullary perfusion and oxygenation after administration of contrast agents. **B**, Radiocontrast stimulates the production of vasodilators (such as prostaglandin [PGI₂] and endothelium-dependent nitric oxide [EDNO]) as well as endothelin and other vasoconstrictors within

the normal kidney. The vasodilators counteract the effects of the vasoconstrictors so that intrarenal vasoconstriction in response to radiocontrast is usually modest and is associated with little or no loss of renal function. However, in situations when there is pre-existing chronic renal insufficiency (CRF) the vasodilator response to radiocontrast is impaired, whereas production of endothelin and other vasoconstrictors is not affected or even increased. As a result, radiocontrast administration causes profound intrarenal vasoconstriction and can cause ARF in patients with CRF. This hypothesis would explain the predisposition of patients with chronic renal dysfunction, and especially diabetic nephropathy, to contrast-induced ARF. (**A**, Adapted from Agmon and Brezis [15], with permission; **B**, from Agmon et al. [16], with permission.)

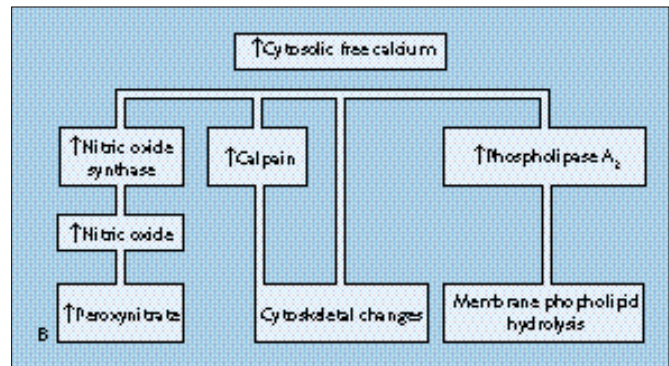
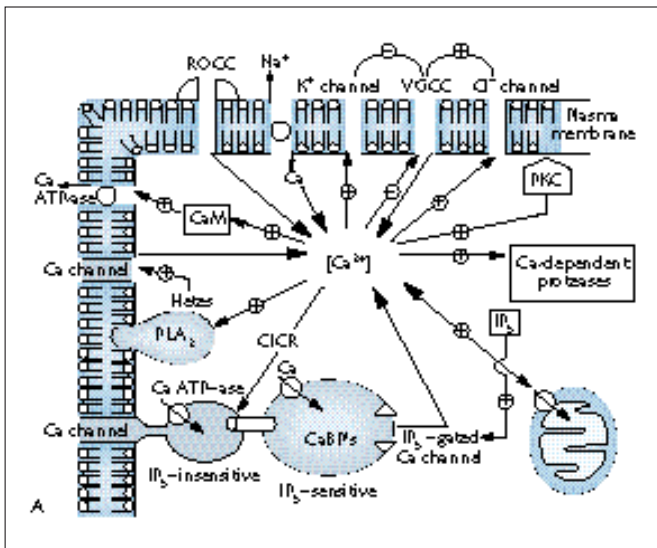


FIGURE 14-21

Cellular calcium metabolism and potential targets of the elevated cytosolic calcium. **A**, Pathways of calcium mobilization. **B**, Pathophysiological mechanisms ignited by the elevation of cytosolic calcium concentration. (**A**, Adapted from Goligorsky [17], with permission; **B**, from Edelstein and Schrier [18], with permission.)

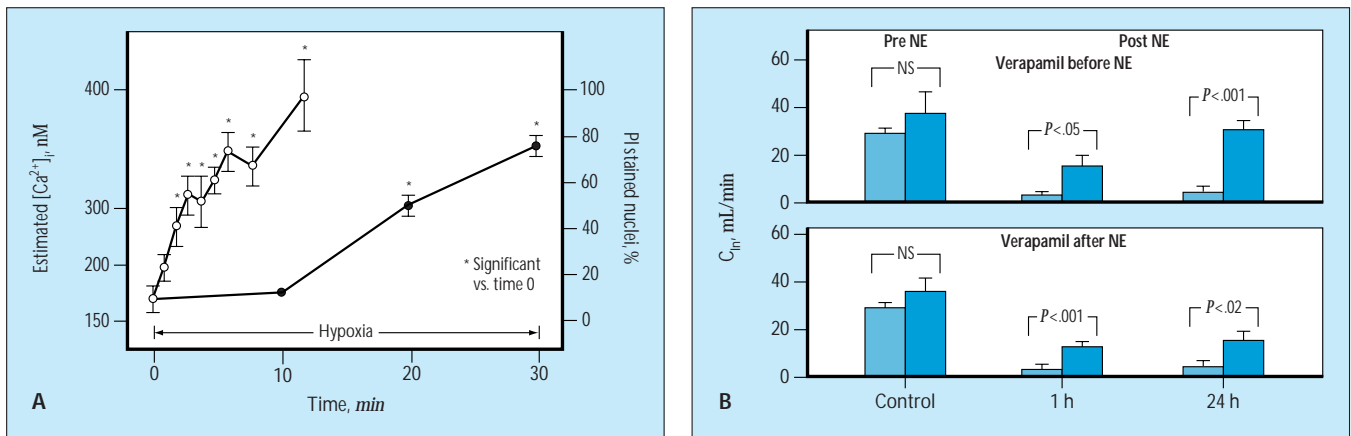


FIGURE 14-22

Pathophysiologic sequelae of the elevated cytosolic calcium (C^{2+}). **A.** The increase in cytosolic calcium concentration in hypoxic rat proximal tubules precedes the tubular damage as assessed by propidium iodide (PI) staining. **B.** Administration of calcium channel inhibitor

verapamil before injection of norepinephrine (*cross-hatched bars*) significantly attenuated the drop in inulin clearance induced by norepinephrine alone (*open bars*). (**A.** Adapted from Kribben *et al.* [19], with permission; **B.** adapted from Burke *et al.* [20], with permission.)

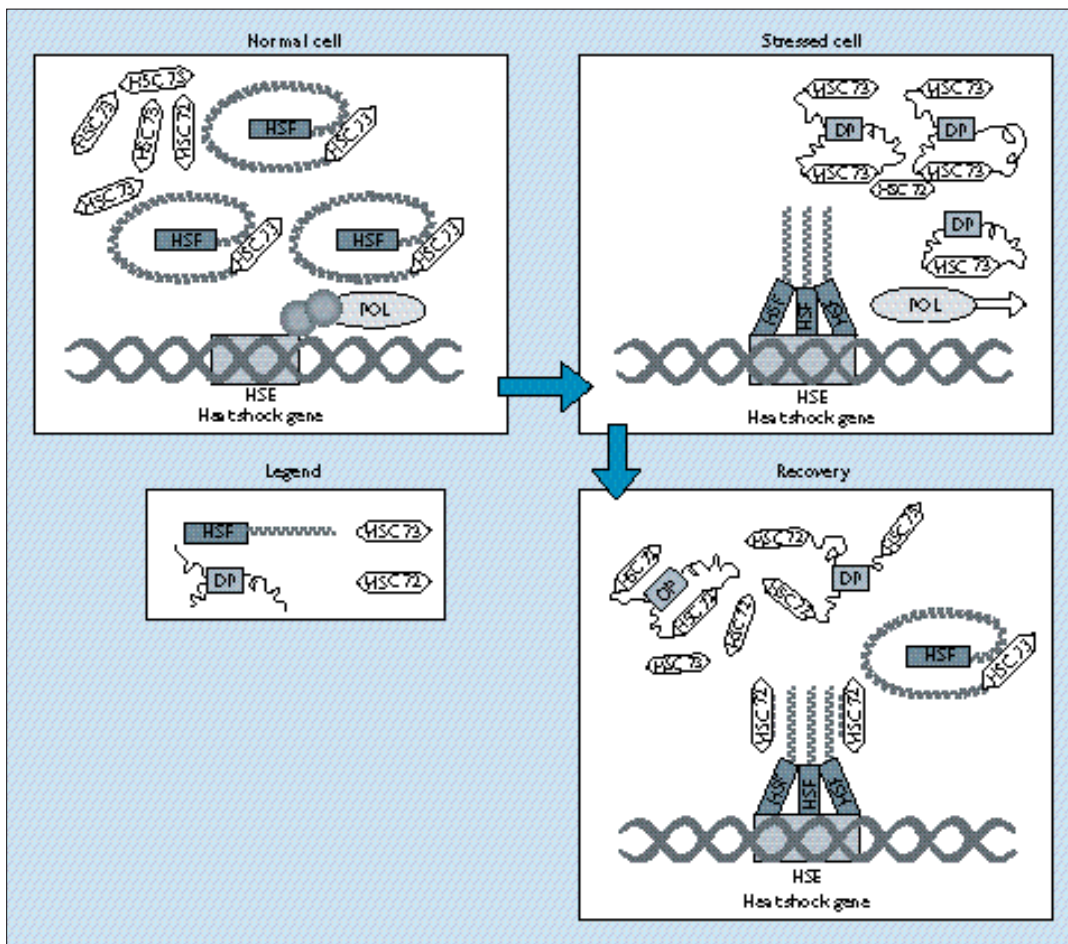


FIGURE 14-23

Dynamics of heat shock proteins (HSP) in stressed cells. Mechanisms of activation and feedback control of the inducible heat shock gene. In the normal unstressed cell, heat shock factor (HSF) is rendered inactive by association with the constitutively expressed HSP70. After hypoxia or ATP depletion, partially denatured proteins (DP) become preferentially associated with HSC73, releasing HSF and allowing trimerization and binding to the heat shock element (HSE) to initiate the transcription of the heat shock gene. After translation, excess inducible HSP (HSP72) interacts with the trimerized HSF to convert it back to its monomeric state and release it from the HSE, thus turning off the response. (Adapted from Kashgarian [21]; with permission.)

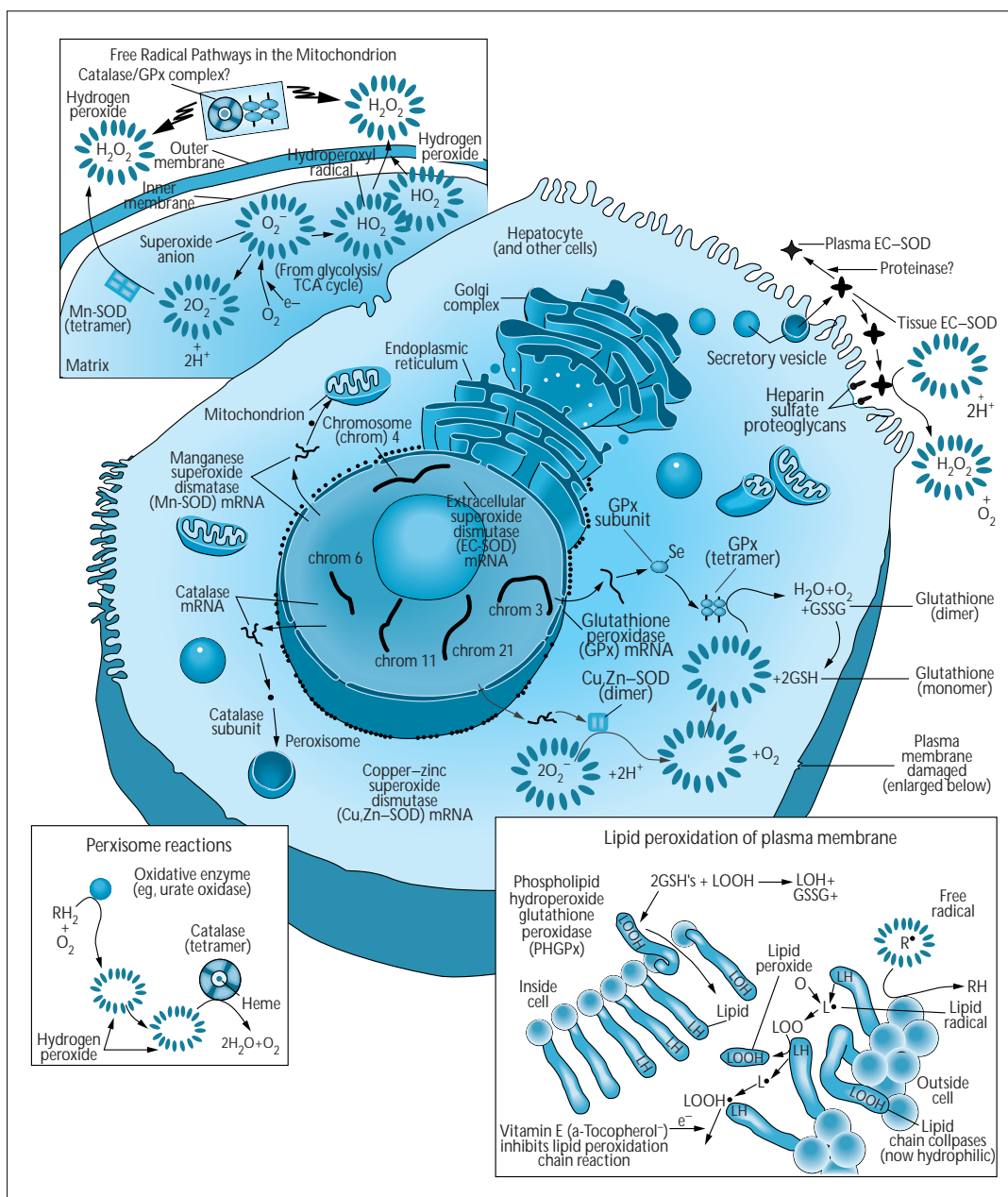


FIGURE 14-24

Cellular sources of reactive oxygen species (ROS) defense systems from free radicals. Superoxide and hydrogen peroxide are produced during normal cellular metabolism. ROS are constantly being produced by the normal cell during a number of physiologic reactions. Mitochondrial respiration is an important source of superoxide production under normal conditions and can be increased during ischemia-reflow or gentamycin-induced renal injury. A number of enzymes generate superoxide and hydrogen peroxide during their catalytic cycling. These include cyclooxygenases and lipoxygenases that catalyze prostanoic and leukotriene synthesis. Some cells (such as leukocytes, endothelial cells, and vascular smooth muscle cells) have NADH/ or NADPH oxidase enzymes in the plasma membrane that are capable of generating superoxide. Xanthine oxidase, which converts hypoxanthine to xanthine, has been implicated as an important source of ROS after ischemia-reperfusion injury. Cytochrome p450, which is bound to the membrane of the endoplasmic reticulum, can be increased by the presence of high concentrations of metabolites that are oxidized by this cytochrome or by injurious events that uncouple the activity of the p450. Finally, the oxidation of small molecules including free heme, thiols, hydroquinones, catecholamines, flavins, and tetrahydropterins, also contribute to intracellular superoxide production. (Adapted from [22]; with permission.)