A. VASODILATORS USED IN EXPERIMENTAL ACUTE RENAL FAILURE (ARF)

Vasodilator	ARF Disorder	Time Given in Relation to Induction	Observed Effect
Propranolol	Ischemic	Before, during, after	↓Scr, BUN if given before, during; no effect if given after
Phenoxybenzamine	Toxic	Before, during, after	Prevented fall in RBF
Clonidine	Ischemic	After	↓Scr, BUN
Bradykinin	Ischemic	Before, during	↑RBF, GFR
Acetylcholine	Ischemic	Before, after	↑RBF; no change in GFR
Prostaglandin E_1	Ischemic	After	↑RBF; no change in GFR
Prostaglandin E_2	Ischemic, toxic	Before, during	↑GFR
Prostaglandin I_2	Ischemic	Before, during, after	↑GFR
Saralasin	Toxic, ischemic	Before	↑RBF; no change in Scr, BUN
Captopril	Toxic, ischemic	Before	↑RBF; no change in Scr, BUN
Verapamil	Ischemic, toxic	Before, during, after	↑RBF, GFR in most studies
Nifedipine	Ischemic	Before	↑GFR
Nitrendipine	Toxic	Before, during	↑GFR
Diliazem	Toxic	Before, during, after	↑GFR; ↓recovery time
Chlorpromazine	Toxic	Before	↑GFR; ↓recovery time
Atrial natriuretic peptide	Ischemic, toxic	After	↑RBF, GFR

BUN—blood urea nitrogen; GFR—glomerular filtration rate; RBF—renal blood flow; Scr–serum creatinine.

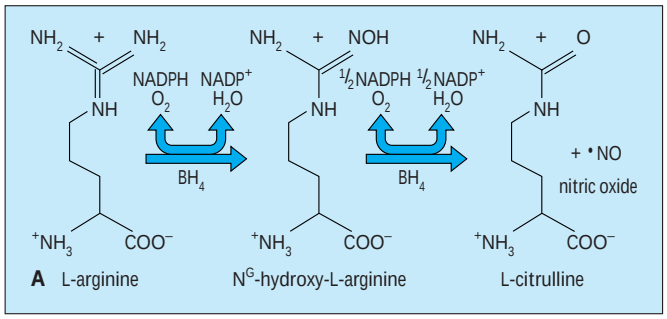
B. VASODILATORS USED TO ALTER COURSE OF CLINICAL ACUTE RENAL FAILURE (ARF)

Vasodilator	ARF Disorder	Observed Effect	Remarks
Dopamine	Ischemic, toxic	Improved V, Scr if used early	Combined with furosemide
Phenoxybenzamine	Ischemic, toxic	No change in V, RBF	
Phentolamine	Ischemic, toxic	No change in V, RBF	
Prostaglandin A_1	Ischemic	No change in V, Scr	Used with dopamine
Prostaglandin E_1	Ischemic	↑RBF, no change v, C_{cr}	Used with NE
Dihydralazine	Ischemic, toxic	↑RBF, no change V, Scr	
Verapamil	Ischemic	↑C_{cr} or no effect	
Diltiazem	Transplant, toxic	↑C_{cr} or no effect	Prophylactic use
Nifedipine	Radiocontrast	No effect	
Atrial natriuretic peptide	Ischemic	↑C_{cr}	

C_{cr}—creatinine clearance; NE—norepinephrine; RBF—renal blood flow; Scr—serum creatinine; V—urine flow rate.

FIGURE 14-15

Vasodilators used in acute renal failure (ARF). **A**, Vasodilators used in experimental acute ARF. **B**, Vasodilators used to alter the course of clinical ARF. (*From* Conger [7]; with permission.)



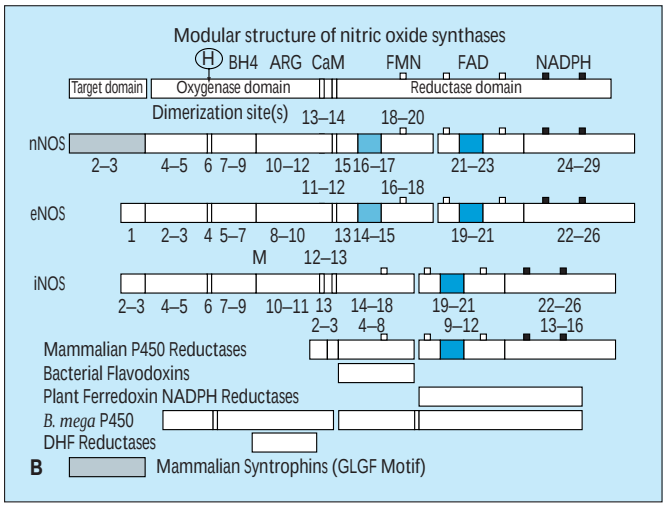
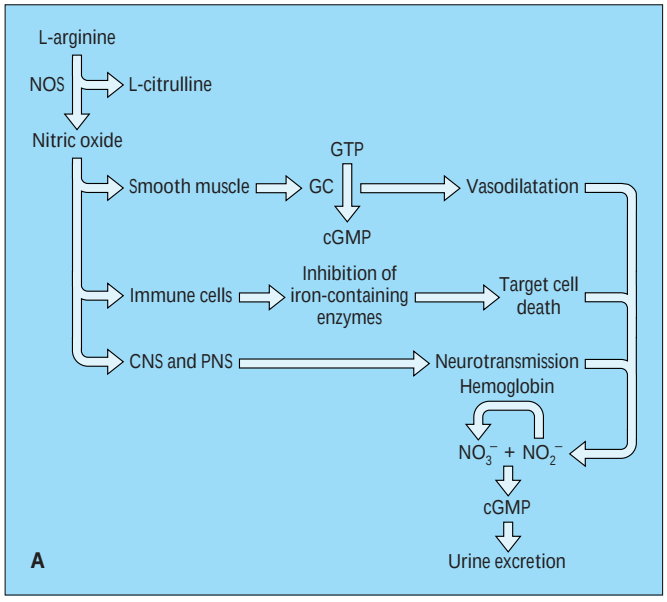
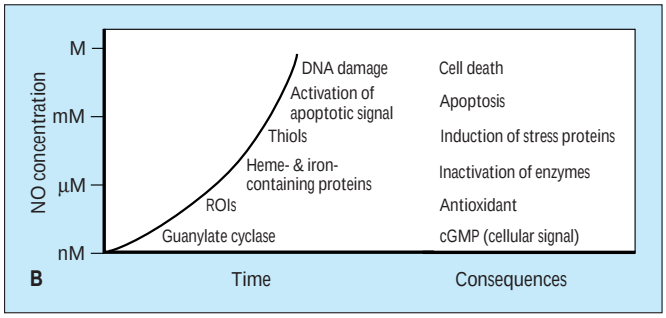


FIGURE 14-16

Chemical reactions leading to the generation of nitric oxide (NO), **A**, and enzymes that catalize them, **B**. (*Modified from* Gross [8]; with permission.)





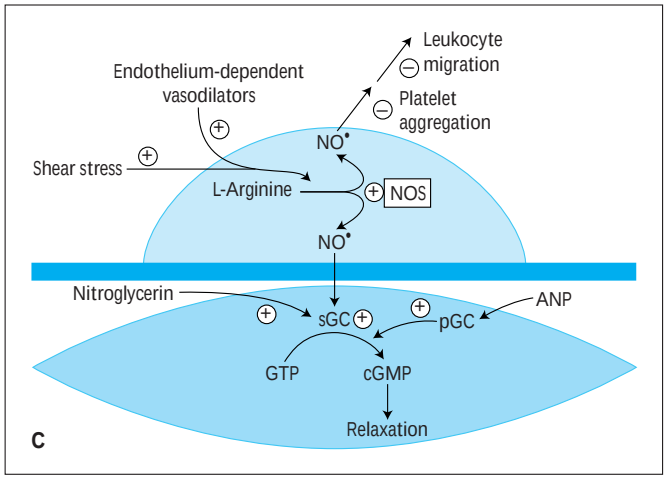


FIGURE 14-17

Major organ, **A**, and cellular, **B**, targets of nitric oxide (NO). **A**, Synthesis and function of NO. **B**, Intracellular targets for NO and pathophysiological consequences of its action. **C**, Endothelium-dependent vasodilators, such as acetylcholine and the calcium ionophore A23187, act by stimulating eNOS activity thereby increasing endothelium-derived nitric oxide (EDNO) production. In contrast, other vasodilators act independently of the endothelium. Some endothelium-independent vasodilators such as nitroprusside and nitroglycerin induce vasodilation by directly releasing nitric oxide in vascular smooth muscle cells. NO released by these agents, like EDNO, induces vasodilation by stimulating the production of cyclic guanosine monophosphate (cGMP) in vascular smooth muscle (VSM) cells. Atrial natriuretic peptide (ANP) is also an endothelium-independent vasodilator but acts differently from NO. ANP directly stimulates an isoform of guanylyl cyclase (GC) distinct from soluble GC (called particulate GC) in VSM. CNS—central nervous system; GTP—guanosine triphosphate; NOS—nitric oxide synthase; PGC—particulate guanylyl cyclase; PNS—peripheral nervous system; ROI—reduced oxygen intermediates; SGC—soluble guanylyl cyclase. (**A**, *From* Reyes *et al.* [9], with permission; **B**, *from* Kim *et al.* [10], with permission.)

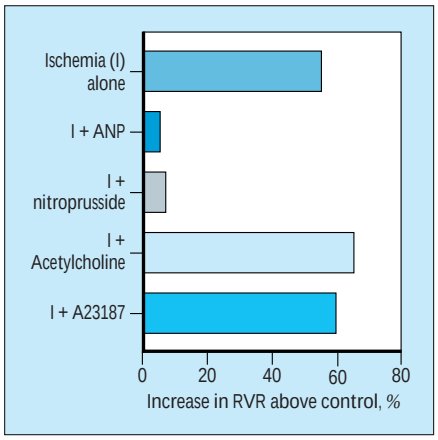
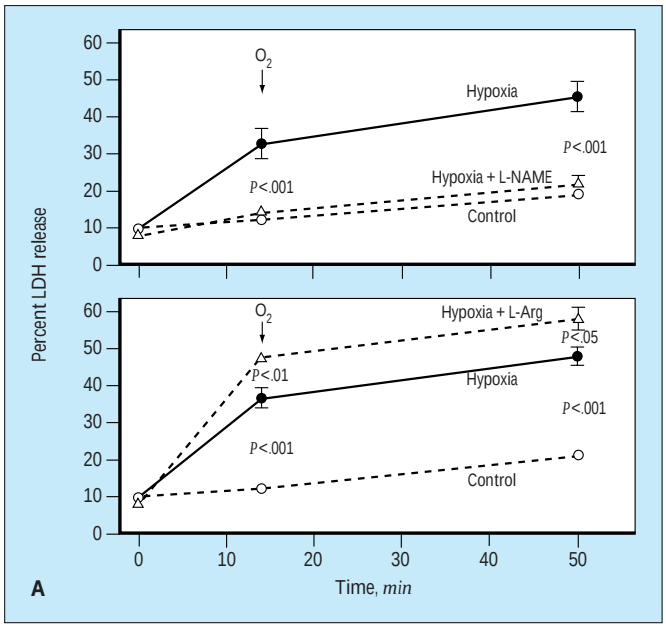
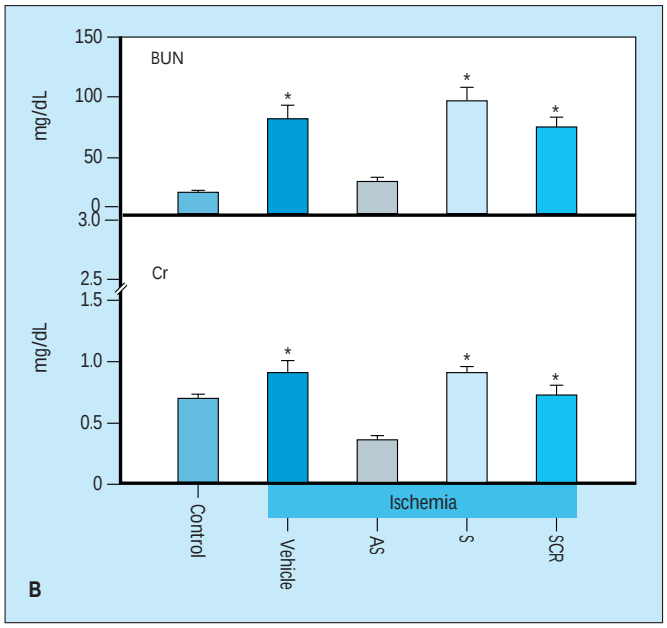


FIGURE 14-18

Impaired production of endothelium-dependent nitric oxide (EDNO) contributes to the vasoconstriction associated with established acute renal failure (ARF). Ischemia-reperfusion injury in the isolated erythrocyte-perfused kidney induced persistant intarenal vasoconstriction. The endothelium-independent vasodilators (atrial natriuretic peptide [ANP] and nitroprusside) administered during the reflow period caused vasodilation and restored the elevated intrarenal vascular resistance (RVR) to normal. In marked contrast, two endothelium-dependent vasodilators (acetylcholine and A23187) had no effect on renal vascular resistance after ischemia-reflow. These data suggest that EDNO production is impaired following ischemic injury and that this loss of EDNO activity contributes to the vasoconstriction associated with ARF. (*Adapted from* Lieberthal [11]; with permission.)





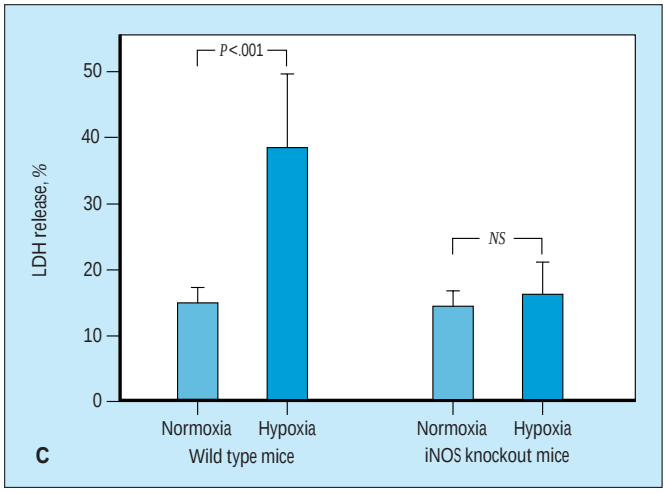


FIGURE 14-19

Deleterious effects of nitric oxide (NO) on the viability of renal tubular epithelia. **A**, Hypoxia and reoxygenation lead to injury of tubular cells (*filled circles*); inhibition of NO production improves the viability of tubular cells subjected to hypoxia and reoxygenation (*triangles* in *upper graph*), whereas addition of L-arginine enhances the injury (*triangles* in *lower graph*). **B**, Amelioration of ischemic injury in vivo with antisense oligonucleotides to the iNOS: blood urea nitrogen (BUN), and creatinine (CR) in rats subjected to 45 minutes of renal ischemia after pretreatment with antisense phosphorothioate oligonucleotides (AS) directed to iNOS or with sense (S) and scrambled (SCR) constructs. **C**, Resistance of proximal tubule cells isolated from iNOS knockout mice to hypoxia-induced injury. LDH—lactic dehydrogenase. (**A**, *From* Yu *et al.* [12], with permission; **B**, *from* Noiri *et al.* [13], with permission; **C**, *from* Ling *et al.* [14], with permission.)