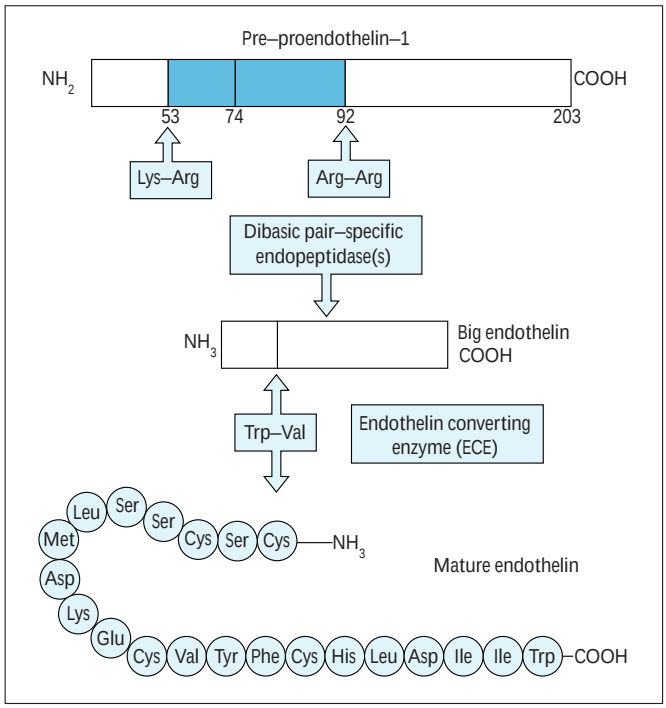

FIGURE 14-9

Biosynthesis of mature endothelin-1 (ET-1). The mature ET-1 peptide is produced by a series of biochemical steps. The precursor of active ET is pre-pro ET, which is cleaved by dibasic pair-specific endopeptidases and carboxypeptidases to yield a 39–amino acid intermediate termed big ET-1. Big ET-1, which has little vasoconstrictor activity, is then converted to the mature 21–amino acid ET by a specific endopeptidase, the endothelin-converting enzyme (ECE). ECE is localized to the plasma membrane of endothelial cells. The arrows indicate sites of cleavage of pre-pro ET and big ET.

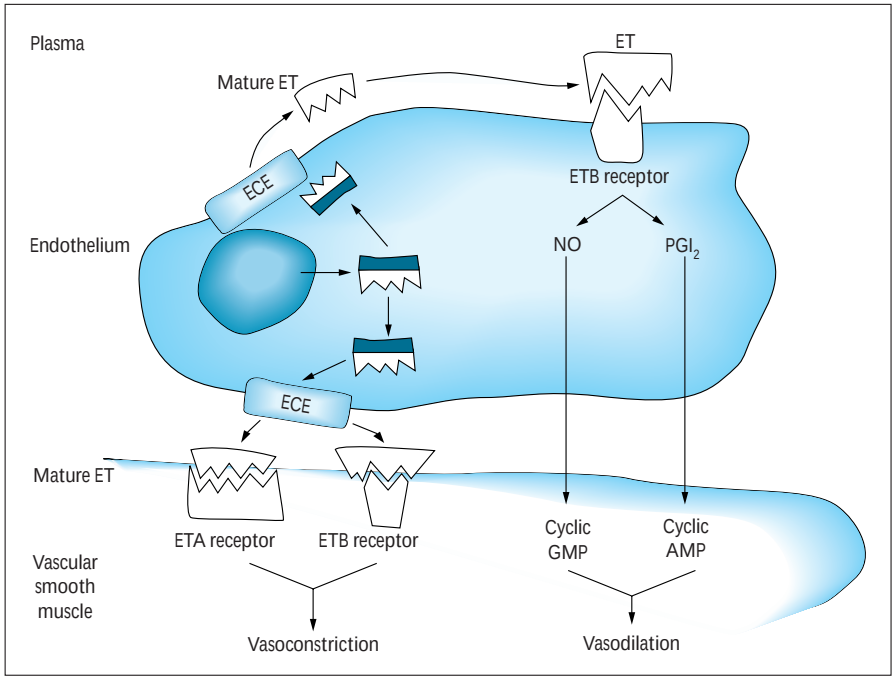

FIGURE 14-10

Regulation of endothelin (ET) action; the role of the ET receptors. Pre-pro ET is produced and converted to big ET. Big ET is converted to mature, active ET by endothelin-converting enzyme (ECE) present on the endothelial cell membrane. Mature ET secreted onto the basolateral aspect of the endothelial cell binds to two ET receptors (ET_A and ET_B); both are present on vascular smooth muscle (VSM) cells. Interaction of ET with predominantly expressed ET_A receptors on VSM cells induces vasoconstriction. ET_B receptors are predominantly located on the plasma membrane of endothelial cells. Interaction of ET-1 with these endothelial ET_B receptors stimulates production of nitric oxide (NO) and prostacyclin by endothelial cells. The production of these two vasodilators serves to counterbalance the intense vasoconstrictor activity of ET-1. PGI_2—prostaglandin I_2.

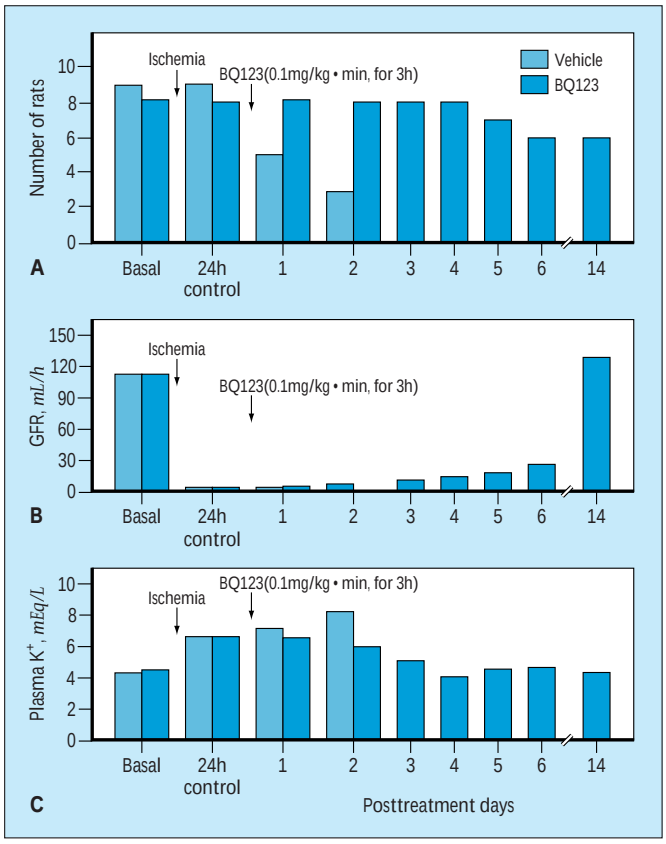

FIGURE 14-11

Endothelin-1 (ET-1) receptor blockade ameliorates severe ischemic acute renal failure (ARF) in rats. The effect of an ET_A receptor antagonist (BQ123) on the course of severe postischemic ARF was examined in rats. BQ123 (*light bars*) or its vehicle (*dark bars*) was administered 24 hours after the ischemic insult and the rats were followed for 14 days. **A**, Survival. All rats that received the vehicle were dead by the 3rd day after ischemic injury. In contrast, all rats that received BQ123 post-ischemia survived for 4 days and 75% recovered fully. **B**, Glomerular filtration rate (GFR). In both groups of rats GFR was extremely low (2% of basal levels) 24 hours after ischemia. In BQ123-treated rats there was a gradual increase in GFR that reached control levels by the 14th day after ischemia. **C**, Serum potassium. Serum potassium increased in both groups but reached significantly higher levels in vehicle-treated compared to the BQ123-treated rats by the second day. The severe hyperkalemia likely contributed to the subsequent death of the vehicle treated rats. In BQ123-treated animals the potassium fell progressively after the second day and reached normal levels by the fourth day after ischemia. (*Adapted from* Gellai *et al*. [5]; with permission.)

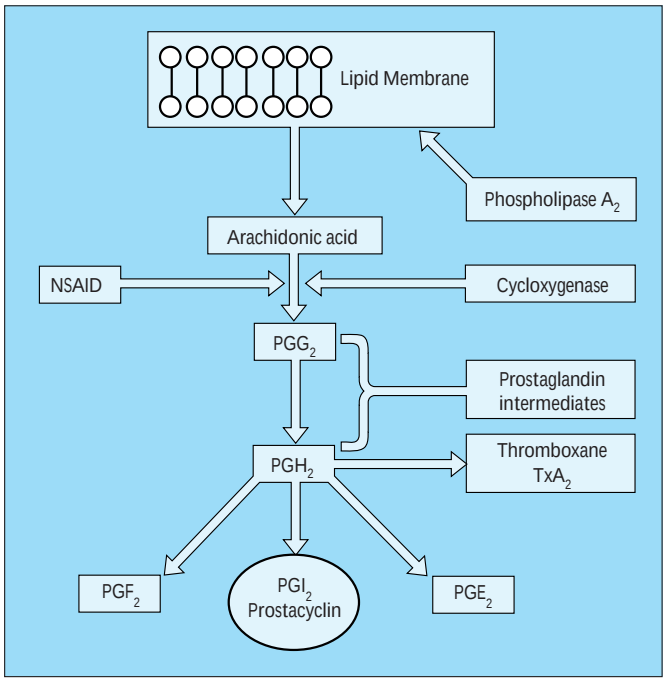

FIGURE 14-12

Production of prostaglandins. Arachidonic acid is released from the plasma membrane by phospholipase A_2. The enzyme cycloxygenase catalyses the conversion of arachidonate to two prostanoid intermediates (PGH_2 and PGG_2). These are converted by specific enzymes into a number of different prostanoids as well as thromboxane (TXA_2). The predominant prostaglandin produced varies with the cell type. In endothelial cells prostacyclin (PGI_2) (*in the circle)* is the major metabolite of cycloxygenase activity. Prostacyclin, a potent vasodilator, is involved in the regulation of vascular tone. TXA_2 is not produced in endothelial cells of normal kidneys but may be produced in increased amounts and contribute to the pathophysiology of some forms of acute renal failure (*eg*, cyclosporine A–induced nephrotoxicity). The production of all prostanoids and TXA_2 is blocked by nonsteroidal anti-inflammatory agents (NSAIDs), which inhibit cycloxygenase activity.

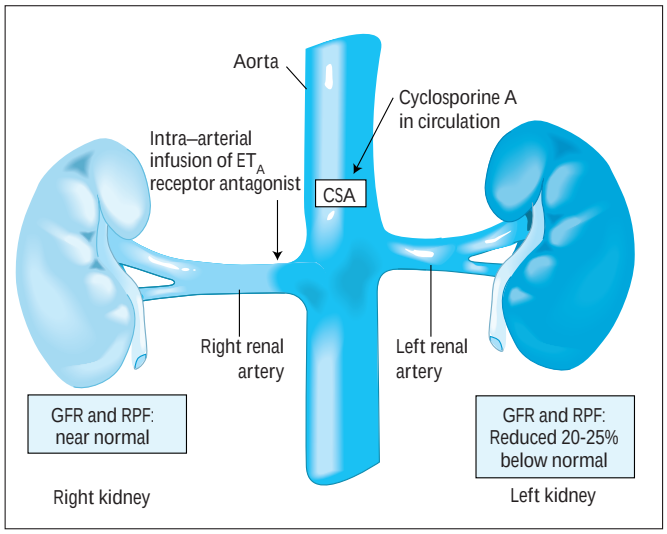

FIGURE 14-13

Endothelin (ET) receptor blockade ameliorates acute cyclosporine-induced nephrotoxicity. Cyclosporine A (CSA) was administered intravenously to rats. Then, an ET receptor anatgonist was infused directly into the right renal artery. Glomerular filtration rate (GFR) and renal plasma flow (RPF) were reduced by the CSA in the left kidney. The ET receptor antagonist protected GFR and RPF from the effects of CSA on the right side. Thus, ET contributes to the intrarenal vasoconstriction and reduction in GFR associated with acute CSA nephrotoxicity. (*From* Fogo *et al.* [6]; with permission.)

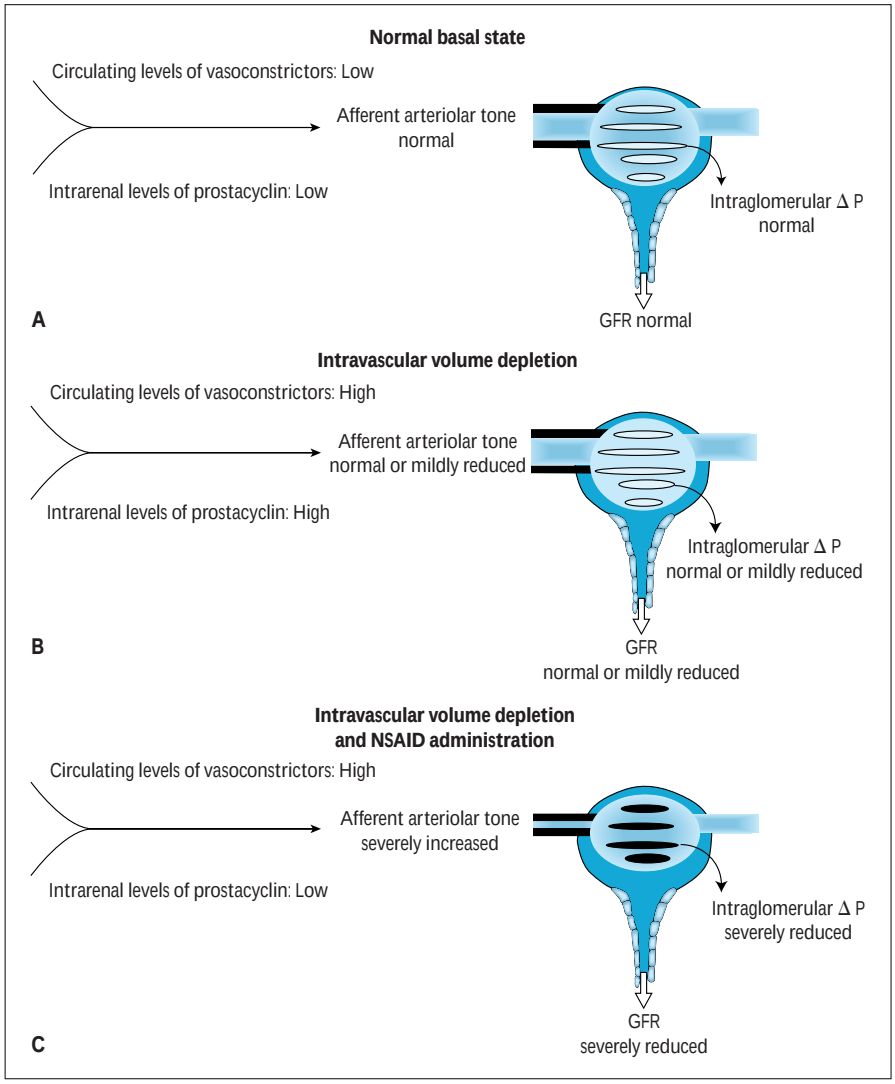

FIGURE 14-14

Prostacyclin is important in maintaining renal blood flow (RBF) and glomerular filtration rate (GFR) in "prerenal" states. **A**, When intravascular volume is normal, prostacyclin production in the endothelial cells of the kidney is low and prostacyclin plays little or no role in control of vascular tone. **B**, The reduction in absolute or "effective" arterial blood volume associated with all prerenal states leads to an increase in the circulating levels of a number of of vasoconstrictors, including angiotensin II, catecholamines, and vasopressin. The increase in vasoconstrictors stimulates phospholipase A_2 and prostacyclin production in renal endothelial cells. This increase in prostacyclin production partially counteracts the effects of the circulating vasoconstrictors and plays a critical role in maintaining normal or nearly normal RBF and GFR in prerenal states. **C**, The effect of cycloxygenase inhibition with nonsteroidal anti-inflammatory drugs (NSAIDs) in prerenal states. Inhibition of prostacyclin production in the presence of intravascular volume depletion results in unopposed action of prevailing vasoconstrictors and results in severe intrarenal vascasoconstriction. NSAIDs can precipitate severe acute renal failure in these situations.