1. SNGFR increases causing increase in delivery of solute to the distal nephron.

2. The composition of filtrate passing the macula densa is altered and stimulates the JGA.

3. Renin is released from specialized cells of JGA and the intrarenal renin angiotensin system generates release of angiotensin II locally.

4. Afferent arteriolar and mesangial contraction reduce SNGFR back toward control levels.

Role of TG feedback in ARF

1. Renal epithelial cell injury reduces reabsorption of NaCl by proximal tubules.

2. The composition of filtrate passing the macula densa is altered and stimulates the JGA.

3. Local release of angiotensin II is stimulated.

4. Afferent arteriolar and mesangial contraction reduce SNGFR below normal levels.

FIGURE 14-5

The tubuloglomerular (TG) feedback mechanism. A, Normal TG feedback. In the normal kidney, the TG feedback mechanism is a sensitive device for the regulation of the single nephron glomerular filtration rate (SNGFR). Step 1: An increase in SNGFR increases the amount of sodium chloride (NaCl) delivered to the juxtaglomerular apparatus (JGA) of the nephron. Step 2: The resultant change in the composition of the filtrate is sensed by the macula densa cells and initiates activation of the JGA. Step 3: The JGA releases renin, which results in the local and systemic generation of angiotensin II. Step 4: Angiotensin II induces vasoconstriction of the glomerular arterioles and contraction of the mesangial cells. These events return SNGFR back toward basal levels. B, TG feedback in ARF. Step 1: Ischemic or toxic injury to renal tubules leads to impaired reabsorption of NaCl by injured tubular segments proximal to the JGA. Step 2: The composition of the filtrate passing the macula densa is altered and activates the JGA. Step 3: Angiotensin II is released locally. Step 4: SNGFR is reduced below normal levels. It is likely that vasoconstrictors other than angiotensin II, as well as vasodilator hormones (such as PGI2 and nitric oxide) are also involved in modulating TG feedback. Abnormalities in these vasoactive hormones in ARF may contribute to alterations in TG feedback in ARF.
Osswald's Hypothesis
- Increased ATP hydrolysis (increased distal Na⁺ load)
- Increased generation of adenosine
- Activation of JGA
- Afferent arteriolar vasoconstriction

Nerve endings

[Na⁺] ATP Adenosine

Adenosine

Renin-containing cells

↓ Renin secretion

ANG II

Vascular smooth muscle

↓ GFR

[Cl⁻]

Signal Transmission

Mediator(s)

Effects

FIGURE 14-6
Metabolic basis for the adenosine hypothesis. A, Osswald's hypothesis on the role of adenosine in tubuloglomerular feedback. B, Adenosine metabolism: production and disposal via the salvage and degradation pathways. (A, Modified from Osswald et al. [2]; with permission.)
**FIGURE 14-8**

Endothelin (ET) is a potent renal vasoconstrictor. Endothelin (ET) is a 21 amino acid peptide of which three isoforms—ET-1, ET-2 and ET-3—have been described, all of which have been shown to be present in renal tissue. However, only the effects of ET-1 on the kidney have been clearly elucidated. ET-1 is the most potent vasoconstrictor known. Infusion of ET-1 into the kidney induces profound and long lasting vasoconstriction of the renal circulation. A, The appearance of the rat kidney during the infusion of ET-1 into the inferior branch of the main renal artery. The lower pole of the kidney perfused by this vessel is profoundly vasoconstricted and hypoperfused. B, Schematic illustration of function in separate populations of glomeruli within the same kidney. The entire kidney underwent 25 minutes of ischemia 48 hours before micropuncture. Glomeruli I are nephrons not exposed to endothelin antibody; Glomeruli II are nephrons that received infusion with antibody through the inferior branch of the main renal artery. SNGFR—single nephron glomerular filtration rate; PFR—glomerular renal plasma flow rate. (From Kon et al. [4]; with permission.)