

## DIURETICS

### 1. TUBULAR EFFECTS OF DIURETICS

Diuretic – an agent which produces an increased urine flow rate

Natriuretic – an agent which increases urinary sodium excretion

All natriuretic drugs are diuretic because increased solute excretion leads to increased water excretion.

#### **A. Diuretic agents affecting the proximal tubule:**

Carbonic anhydrase inhibitors (acetazolamide) prevent the normal breakdown of carbonic acid and, therefore, diminish bicarbonate reabsorption. Since the NaH antiporter is also involved in NaCl reabsorption, these agents also inhibit proximal tubule NaCl reabsorption. By diminishing sodium reabsorption, the osmotic gradient for water reabsorption is decreased. This leads to an increased delivery of NaHCO<sub>3</sub>, NaCl, and water from the proximal tubule to the remaining nephron. The thick ascending limb of Henle is well adapted to handling an increased load of NaCl, therefore, much of the increased delivery of NaCl is reabsorbed in the thick ascending limb of Henle. The rest of the nephron is not geared for bulk reabsorption of NaHCO<sub>3</sub>. The net result is moderate increase in sodium and bicarbonate in the urine along with an increase in urinary flow rate (water excretion).

#### **B. Osmotic diuretics:**

Substances which are filtered at the glomerulus but are not completely reabsorbed will act as osmotic diuretics. Examples are mannitol and glucose (when glucose has exceeded its maximum reabsorption capacity). Glucose is reabsorbed via a sodium coupled receptor which is saturable. Thus, when the filtered load of glucose exceeds the transport maximum of the proximal tubule for glucose, glucose becomes a non-reabsorbable osmotically active particle. This increase in osmotic activity attenuates the osmotic gradient for water reabsorption. Due to their effects on tubular fluid osmolality, osmotic diuretics also impair NaCl reabsorption in the proximal tubule and thick ascending limb of Henle. The net result is that osmotic diuretics are potent diuretics which lead to increased excretion of water and NaCl.

#### **C. Loop diuretics (Furosemide):**

Loop diuretics must enter the tubular fluid to reach their site of action, which is the thick ascending limb of Henle. These diuretics block the luminal receptor which is responsible for the reabsorption of 1 sodium, 1 potassium, in conjunction with 2 chloride ions. Since the thick ascending limb is responsible for about 20% of the sodium chloride reabsorption, loop diuretics are extremely potent diuretics. They lead to increased sodium, potassium, chloride and water excretion.

#### **D. Thiazide diuretics (Hydrochlorothiazide):**

These diuretics must enter the tubular fluid to reach their site of action in the early distal convoluted tubule. These diuretics block the luminal receptor which functions as an electroneutral sodium chloride transporter. The distal convoluted tubule is responsible for about 5% of the total sodium chloride reabsorption, thus, thiazide diuretics are of moderate potency. They lead to increased sodium, potassium, chloride, and water excretion.

#### **E. The effect of solute excretion on urinary flow rate:**

Increased solute excretion (for example, increased NaCl excretion) leads to an increased urinary flow rate. The major mechanism for this is that the solute which is being excreted in increased amounts will be present in the tubular fluid in the collecting duct. Since the solutes are osmotically active, this will decrease the osmotic gradient for water reabsorption from the collecting duct to the interstitium. Thus, water excretion increases. This effect can have marked importance in patients who have abnormal urinary concentrating or diluting ability. In this situation changes in solute excretion will lead to marked changes in urinary flow rate.

**F. Diuretics acting in the collecting duct:**

These agents act by either blocking the sodium channel in the luminal membrane (amiloride) or by acting as competitive antagonists for the cytoplasmic actions of aldosterone (spironolactone). The net result of either of these effects is to lead to a mild increase in sodium excretion. Since less sodium is being reabsorbed in the collecting duct, the lumen has a less negative potential, therefore, potassium secretion and hydrogen ion secretion are diminished. Thus, in contrast to diuretics which act before the collecting duct, these diuretics lead to decreased potassium secretion.

**G. Atrial natriuretic peptides (ANP):**

Small peptide hormones released primarily by the cardiac atria in response to increased atrial stretch, such as seen in volume expansion. ANP binds to receptors in the medullary collecting duct and lead to increased intracellular cyclic GMP. These changes lead to decreased sodium reabsorption. Increased solute excretion leads to increased water excretion. There is no change in the rate of potassium excretion.

**H Diuretic effects on potassium excretion:**

Diuretic agents that act at the proximal tubule (acetazolamide), loop of Henle (furosemide), distal convoluted tubule (thiazide), and osmotic diuretics lead to increased potassium excretion. Each of these diuretic agents increase delivery of sodium and filtrate to the cortical collecting duct, the major site of potassium secretion, leading to increased urinary potassium excretion. Diuretics that act at the cortical collecting duct decrease potassium excretion. ANP, acting at the medullary collecting duct has no effect on potassium excretion.