A 27-year-old patient presents at her obstetrician’s office for her first prenatal visit at 26 weeks gestation. She has no medical history and has had an uncomplicated pregnancy. Her examination is normal other than glycosuria noted on the urine dipstick. A 1-hour glucose challenge test is performed along with her other prenatal laboratories, and they are all normal. The obstetrician diagnoses the glycosuria as a normal physiologic response to the increased glomerular filtration rate (GFR) of pregnancy.

- Where in the renal glomerulus-tubule structure is glucose reabsorbed actively (secondary active transport)?

- What other solutes are reabsorbed by a secondary active process?

- With what is glucose cotransported in the proximal tubule?
ANSWERS TO CASE 22: RENAL TUBULE ABSORPTION

Summary: A 27-year-old pregnant woman presents at 26 weeks gestation with glycosuria and a normal diabetic screen.

◆ **Location of glucose reabsorption:** Proximal tubule.

◆ **Other actively reabsorbed solutes:** Organic acids, amino acids, proteins and peptides, phosphate, and sulfate.

◆ **Cotransporter with glucose:** Sodium.

**CLINICAL CORRELATION**

Glycosuria is present when the filtered load of glucose in the kidney is too large to be reabsorbed. This can be seen in patients with diabetes. The glycosuria acts as an osmotic diuretic and leads to the common symptoms of uncontrolled diabetes: urinary frequency, nocturia, and frequent thirst. During pregnancy, several factors influence glucose reabsorption in the kidney. At that time there is an increased GFR that increases the filtered load of glucose. Lactose and galactose will also be present in the urine in addition to glucose. The increase in GFR and filtered glucose load are normal changes that result in glycosuria during pregnancy. The presence of glycosuria is not suggestive of gestational diabetes, and a 1-hour diabetic screen must be performed to rule out that disease.

**APPROACH TO RENAL TUBULE TRANSPORT**

**Objectives**

1. Understand the function of the proximal tubule.
2. Know the importance of sodium reabsorption.
3. Describe the role of sodium with reabsorption of organic acids, amino acids, and proteins.

**Definitions**

**Glycosuria:** A condition characterized by the appearance of glucose in the urine.

**Tubular transport maximum (Tm):** The maximum rate of transport for a substance (eg, TmG denotes the maximum reabsorptive rate of glucose).

**DISCUSSION**

Most of the fluid filtered at the glomerulus is reabsorbed along the length of the nephron and collecting ducts (see Figure 22-1 for the parts of the glomerulus,
Approximately 60% to 70% of the filtered fluid is reabsorbed in the proximal tubule. The primary transport process underlying fluid reabsorption is active sodium reabsorption. Water and many other filtered solutes then are reabsorbed passively as an isosmotic reabsorbate.

Sodium ion is reabsorbed actively by the proximal tubule cells. The driving force for reabsorption is the Na⁺ pump (also called the Na⁺-K⁺ exchange pump), which is a Na⁺-K⁺-ATPase. The Na⁺ pump actively extrudes Na⁺.
across the basolateral membrane in exchange for K+, thereby keeping the
[Na+] concentration inside the cell low and [K+] high. The high [K+] generates
a diffusion potential across the basolateral membrane that is responsible for
the cell’s negative membrane potential (−70 mV) across the basolateral and
luminal cell borders. The low intracellular [Na+] concentration and the cell’s
negative membrane potential create a favorable gradient for passive entry of
Na+ across the luminal membrane into the cell. The Na+ then is extruded
actively across the basolateral membrane, giving rise to Na+ reabsorption.
Chloride and bicarbonate ion are reabsorbed passively either through the cell
or through the tight junctions between the cells (the proximal tubule has
“leaky” tight junctions), providing a balance of charge. **The tissue is very
leaky to water** so that as solute is reabsorbed through the cell into the inter-
stitial space, water follows passively by osmotic coupling to the solute, mov-
ing through the cells or through the “leaky” tight junctions between the cells.

The entry step for Na+ across the luminal cell membrane is normally a cou-
pled process. The **two most dominant transport processes are Na+-H+ ex-
change**, which is important for Na+ reabsorption and acid–base balance, and
**Na+-glucose cotransport**, which is important for both Na+ and glucose reab-
sorption. Both processes are passive steps that are driven by the Na+ gradient into
the cell (set up by the Na+ pump). For glucose, the downhill gradient for Na+ entry
across the luminal membrane can drive the cellular glucose concentration to
higher levels than that apparent in the luminal fluid, thereby appearing to be
active transport, but only secondary to Na+ transport (see Figure 1-2). Hence, glu-
cose entry often is referred to as secondary active transport even though the
entry step is passive. Once inside the cell, glucose is transported passively across
the basolateral membrane by a facilitated diffusion process (passive glucose
transporter) into the interstitial space and taken up into the peritubular capillaries.

Under normal conditions, all filtered glucose is reabsorbed, except for
trace quantities, from the tubular lumen of the proximal tubule, utilizing the Na+-
glucose cotransport process at the luminal border. However, both Na+ and glu-
cose must bind to specific, but saturable, sites on the Na+-glucose cotransport
carrier protein, making glucose reabsorption saturable. Hence, under condi-
tions of elevated plasma glucose levels, such as in diabetes mellitus, or an
increased glomerular filtration rate, such as in pregnancy, the filtered glucose
load can exceed the capacity for glucose transport; that is, the Na+ glucose
cotransporters become saturated, leaving un-reabsorbed glucose behind in the
tubular fluid which is swept away into the final urine (glycosuria). The maximum rate of glucose reabsorption (Figure 22-2) is defined as the tubular
transport maximum for glucose (TmG), whereas the plasma concentration at
which glucose first begins to appear in the urine is defined as the renal plasma
threshold. In the presence of un-reabsorbed glucose, the “trapped” glucose will
act as an osmotic solute, leading to an osmotic diuresis. The associated diuresis
can be particularly problematic in patients with diabetes mellitus.

The reabsorption of other organic solutes in the proximal tubule also is cou-
ped to Na+ as a Na+-solute cotransporter at the luminal cell membrane,
similar to what has been described for glucose. Both sugars, such as galactose, and most amino acids, such as glutamate and glycine, are cotransported with Na\(^+\) and display both a tubular transport maximum and a renal plasma threshold (the transport of some amino acids, such as lysine and proline, is not Na\(^+\) dependent). Galactose can compete with glucose for binding and transport by the Na\(^+\)-glucose carrier so that with elevated plasma levels of galactose, such as in pregnancy, galactose can contribute to appearance of glucose in the urine.

The proximal tubule is also the site of reabsorption of certain organic acids, with the most dominant normally being lactate anion. Two Na\(^+\)-dependent cotransport process at the luminal membrane appear to underlie organic acid reabsorption: one specific for monocarboxylates such as lactate, pyruvate, acetoacetate, and β-hydroxybutyrate and the other for di- and tricarboxylates such as malate, succinate, and citrate. Both are Na\(^+\)-organic solute cotransporters and hence require Na\(^+\) for uptake. Once inside the cell, the carboxylates exit the cell by means of a variety of exchange processes. Other organic acids, such as urate, an end product of purine catabolism, are both secreted and reabsorbed in the proximal tubule; both processes are Na\(^+\)-independent, with the reabsorptive mechanisms dominating. Finally, the proximal tubule is the site of secretion of numerous organic anions (para-aminohippurate, oxalate) and cations (choline, guanidine) by separate, saturable transport processes that often involve anion exchange processes that are Na\(^+\)-independent.

Figure 22-2. Tm\(_G\): tubular transport maximum for glucose; RPT: renal plasma threshold for glucose.
Filtered peptides and proteins are also reabsorbed almost entirely in the proximal tubule. However, their reabsorption is not coupled directly to Na⁺. Small peptides such as angiotensin II are first hydrolyzed by brush-border peptidases to their constituent amino acids, and the amino acids then are reabsorbed via the usual Na⁺-amino acid cotransport processes. Larger peptides and proteins such as myoglobin and albumin bind to the luminal membrane and enter the cell by receptor-mediated endocytic processes and are delivered to lysosomes for degradation. Some filtered inorganic anions, such as sulphate and phosphate, also are reabsorbed in the proximal tubule via a Na⁺ cotransport process; hence, their transport can be defined by a Tm and renal plasma threshold.

COMPREHENSION QUESTIONS

[22.1] An individual has adult-onset diabetes. She has high levels of glucose in the urine and is experiencing a brisk diuresis. The appearance of glucose in the urine is a consequence of which of the following processes in the proximal tubule?

A. Inhibition of Na⁺-K⁺-ATPase (Na⁺ pump)
B. Saturation of the Na⁺-glucose cotransporter
C. Saturation of the Na⁺-H⁺ exchanger
D. Stimulation of glucose secretion
E. Stimulation of glycogen breakdown

[22.2] A student under stress has been feeling light-headed, especially after standing, and has developed a brisk diuresis. He has the smell of acetone on his breath. Upon admission to the emergency room, he is diagnosed with diabetic ketoacidosis, which is accompanied by extreme hypovolemia, supposedly because of the brisk diuresis. The brisk diuresis is a consequence of which of the following?

A. High levels of glucose in the tubular fluid/urine
B. Increased glomerular filtration rate
C. Suppression of arginine vasopressin secretion
D. Suppression of aldosterone secretion
E. Decreased angiotensin II plasma levels

[22.3] A 23-year-old man is brought into the emergency center because of cocaine intoxication. His urine is “tea” colored as a result of breakdown of skeletal muscle by the cocaine, so-called rhabdomyolysis. Which of the following describes the fate of myoglobin in the renal tubule?

A. Absorbed in the proximal tubule by active transport by sodium cotransport
B. Absorbed in the proximal tubule by receptor-mediated endocytosis
C. Absorbed in the distal tubule by facilitated diffusion
D. Not absorbed and excreted in the urine
**Answers**

[22.1] **B.** In diabetes mellitus, in which plasma glucose levels are markedly elevated, the high glucose load being filtered (with an elevated concentration) can exceed the capacity of the luminal Na⁺-glucose cotransporter to reabsorb glucose (ie, the carrier is saturated). The excess glucose that is not reabsorbed is trapped in the tubular fluid because no transport pathways are present in later nephron segments to reabsorb this hexose. Hence, glycosuria will develop.

[22.2] **A.** In diabetic ketoacidosis, plasma levels of glucose are elevated, leading to an excess filtered load of glucose. The increased rate of filtration of glucose can exceed the capacity of the Na⁺-glucose cotransporter in the proximal tubule to reabsorb all the glucose. The excess glucose that is not reabsorbed will be retained in the tubular lumen and generate a solute diuresis.

[22.3] **B.** Larger peptides and proteins such as myoglobin and albumin bind to the luminal membrane and enter the cell by receptor-mediated endocytic processes and are delivered to lysosomes for degradation. Myoglobin, if crystallized in the renal tubules, can lead to a toxic effect, sometimes even renal failure. Cocaine can induce numerous toxic effects, including rhabdomyolysis. Intravenous hydration is important to increase the solubility of the myoglobin.

**PHYSIOLOGY PEARLS**

- If the filtered load of glucose exceeds the capacity of the renal tubule to reabsorb the glucose, the glucose left behind is “trapped” in the tubular lumen and acts as an osmotic solute, leading to an osmotic diuresis.
- The reabsorption of glucose is coupled to Na⁺ via a luminal membrane Na⁺-glucose cotransporter. The favorable downhill electrochemical gradient for Na⁺ entry can drive influx of glucose up its chemical gradient to elevated levels inside the cell, thereby appearing to be an active influx of glucose (even though it is passive), giving rise to what is termed secondary active transport of glucose.
- Many amino acids are reabsorbed in the proximal tubule by Na⁺-amino acid cotransport processes, whereas others are reabsorbed by Na⁺-independent transport processes.
- Oligopeptides are reabsorbed in the proximal tubule by first being metabolized to their constitutive amino acids by luminal membrane peptidases and then being transported by Na⁺-amino acid cotransporters and Na⁺-independent amino acid transporters into the cell.
- Large peptides and proteins are reabsorbed in the proximal tubule by receptor-mediated endocytosis.
REFERENCES
