

MODULE 04

RENAL PHYSIOLOGY

Please note: This course was designed to be interacted and engaged with using the online modules. This **Module Companion Guide** is a resource created to complement the online slides. If there is a discrepancy between this guide and the online module, please refer to the module.

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INTRODUCTION

Please see the online learning module for the full experience of interactions within this document.

INTRODUCTION

This content was retrieved from Introduction, Slide 1 of 4 of the online learning module.

Homeostasis within the body is controlled, in large part, by the kidneys. These organs are responsible for the regulation of electrolyte composition, volume, osmolarity, and p H of the internal environment. Additionally, the kidneys work to eliminate all the waste products from bodily metabolism with the exception of carbon dioxide which is removed by respiration. These waste products are substances the body does not need, such as metabolic wastes and excess quantities of salt or water, and are eliminated through the urine. All useful substances, such as glucose and phosphates, are conserved.

Throughout this module, we will explore the huge responsibility of the kidneys. We'll start by examining their anatomy and physiology, and then continue on to learn about their role in the balance and regulation of substances such as water, sodium, plasma, electrolytes, glucose, and phosphate.

Review the icons used in this course:

A Closer Look

These are detailed descriptions or examples that are beyond the scope of this course, but are designed to supplement your learning.

Test Your Knowledge

Throughout the modules, you are given many opportunities to test yourself on the material presented.

Study Tips & Tools

These include study tools, such as mnemonics and acronyms, and study tips aimed to guide your studying.

Clinical Application

Clinical examples and pathologies, although beyond the scope of the course, are included to expand your understanding.

LEARNING OUTCOMES

This content was retrieved from Introduction, Slide 2 of 4 of the online learning module.

By the end of this module, you will be able to:

1. Describe the major structures of a juxtamedullary nephron and discuss the importance of each section with respect to reabsorption and secretion.
2. Describe blood flow through the kidneys and its physiological importance in the generation of urine.
3. Using your knowledge of osmotic gradients, describe how the kidney can make urine either more dilute or more concentrated than other bodily fluids.

- Using dehydration as an example, describe the physiological responses and processes that occur in order to reduce water loss through urine production.

MODULE ASSIGNMENTS

This content was retrieved from Introduction, Slide 3 of 4 of the online learning module.

Each module in this course has associated assessments that relate to the content you will be learning. Some of these assessments may only be relevant to one module whereas others will build upon concepts you will learn as you advance through the course. More details about each assignment can be found in the assignment description on the course website.

Independent Research Assignment - Refer to page 7

Case Study Discussion Board Series - Refer to page 7

Activities throughout the Module:

Note that text responses and interactions will not be graded unless otherwise notified. However, they are recorded in the module and viewable by your instructor.

ASSIGNMENT: TERM REPORT

Subpage of Introduction, Slide 3 of 4 – Independent Research Assignment 1/1

This purpose of this report is to assess each student's foundational knowledge of systems physiology, and to provide the opportunity for students to complete independent research on pathophysiology. Students will choose from a list of provided diseases and complete independent research to submit a report (max. 750 words) summarizing the disease, physiology (normal), pathophysiology of the disease, and impact of treatment on the physiology/pathophysiology.

Navigate to the assignment description on the course website for more details.

ASSIGNMENT: CASE STUDY DISCUSSION BOARD SERIES

Subpage of Introduction, Slide 3 of 4 – Case Study Discussion Board Series 1/1

Students will be placed in small groups and assigned biweekly case studies and a corresponding set of questions. Each student is required to answer at least one of the associated questions, and respond to at least one peer's post. Students will be marked on the quality of their posts and their efforts to participate in discussion with their group members.

Navigate to the assignment description on the course website for more details.

MODULE OUTLINE

This content was retrieved from Introduction, Slide 4 of 4 of the online learning module.

Section 01: Introduction to Renal Physiology and Water Balance

Section 02: Overview of the Kidneys

Section 03: Glomerular Filtration

Section 04: Tubular Reabsorption

Section 05: Tubular Secretion

Section 06: Plasma Clearance and Urine Excretion

SECTION 01: INTRODUCTION TO RENAL PHYSIOLOGY AND WATER BALANCE

SECTION 01: INTRODUCTION TO RENAL PHYSIOLOGY AND WATER BALANCE

This content was retrieved from Section 01, Slide 1 of 16 of the online learning module.

By the end of Section 01, you should be able to:

1. Identify the major fluid compartments and describe how they are interrelated.
2. Compare and contrast short-term vs long-term control of the extracellular fluid.
3. Describe the differences between isotonic, hypertonic, and hypotonic, and how cells in each of these solutions would be affected.
4. Describe the pathways involved in the regulation of water balance in terms of intake and output.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 14: Pages 607-619

INTRODUCTION

This content was retrieved from Section 01, Slide 2 of 16 of the online learning module.

The kidneys are involved in many homeostatic functions including regulating electrolytes, acid-base control, blood volume control, and the regulation of blood pressure. This module, however, will only focus on how the kidneys maintain the stability of the extracellular fluid (ECF) volume, electrolyte composition, and osmolarity. In order to explore these topics, we must first have a good understanding of water balance, as this ultimately is the primary goal of the kidneys.

This section of the module will introduce you to the basic concepts of water balance and electrolytes.

From there, we will be able to expand on and extend these concepts to understand how the kidneys regulate both electrolytes and water.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

CONCEPT OF WATER BALANCE

This content was retrieved from Section 01, Slide 3 of 16 of the online learning module.

Every cell in the body requires a well-regulated environment in order to survive and function. Body water plays a large role in creating this environment, which is actually comprised of two major compartments.

Learn about these compartments.

Intracellular Fluid (ICF)

This is the fluid within cells and comprises about two thirds of total body fluid.

Alt Text: *A graph depicting the composition of total body fluid.*

Extracellular Fluid (ECF)

This is the fluid surrounding the cells which includes the plasma, the interstitial fluid, lymph, and **transcellular fluid*** (such as cerebrospinal fluid) and comprises about one third of total body fluid. The plasma is about one fifth of the ECF, the interstitial fluid is about four fifths of the ECF, and the lymph and the transcellular fluid are considered negligible.

When we talk about the major body compartments for water (fluid) there are three key pools: ICF, plasma, and interstitial fluid. These pools remain distinct due to the presence of “barriers” between them.

Definition*:

Transcellular Fluid: The portion of total body water contained within epithelial lined spaces.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

BARRIERS BETWEEN BODY-FLUID COMPARTMENTS

This content was retrieved from Section 01, Slide 4 of 16 of the online learning module.

Several barriers separate the body-fluid compartments. This limits the movement of water and solutes between the various compartments to differing degrees.

Learn about these barriers.

Barriers between the plasma and the interstitial fluid

You may recall from Module 06 that the plasma and the interstitial fluid are separated by the blood vessel walls. However, at the level of the capillaries, water and everything else in the plasma (except proteins) can freely exchange with the interstitial fluid. Because of this, the composition of the plasma and the interstitial fluid are essentially identical, except for the plasma proteins, as seen in the graph. Consequently, any change in one of these compartments is quickly reflected in the other compartment.

Barriers between the intracellular fluid and the ECF

This barrier is the plasma membrane that surrounds each cell in the body. The ICF contains proteins that do not exchange with the ECF.

Take a moment to analyze the graph to see which proteins do not exchange with the ECF.

There is an unequal distribution of ions across this barrier. For example, the concentration of K^+ is greater in the ICF while the concentration of Na^+ is greater in the ECF. This is because the barrier does

not allow the passive movement of either ICF or ECF constituents across the plasma membrane, preventing them from equilibrating through the process of diffusion.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

ECF VOLUME AND OSMOLARITY

This content was retrieved from Section 01, Slide 5 of 16 of the online learning module.

All exchanges of water and other constituents between the ICF and the external world are dependent upon the ECF. Even though cells tightly regulate their own ICF, it can be said that overall control of fluid balance is dependent upon regulating the ECF.

In order to maintain fluid balance in the body, two factors are regulated.

Learn about these two factors.

ECF Volume

This is closely regulated to maintain blood pressure. The maintenance of salt balance is important in the long-term regulation of ECF volume.

ECF Osmolarity

This is closely regulated to prevent the swelling or shrinkage of cells.

We will be exploring these two factors in greater detail in the upcoming slides.

CONTROL OF ECF VOLUME

This content was retrieved from Section 01, Slide 6 of 16 of the online learning module.

ECF volume directly influences blood pressure by changing plasma volume. Increasing ECF volume will increase plasma volume, and thus increase arterial blood pressure. Consequently, there are mechanisms in place to adjust blood pressure until the ECF volume is returned to normal values.

Review the short and long term control measures that accomplish this.

Short-term Control Factors**The Baroreceptor Reflex**

Baroreceptors are mechanoreceptors that are located in the carotid artery and the aortic arch (areas within major arteries of the body), and they detect changes in arterial blood pressure. Through the effects of the autonomic nervous system on the heart and blood vessels, the baroreceptor reflex regulates blood pressure. When pressure falls too low, **cardiac output*** and **total peripheral* resistance** will increase to raise blood pressure. When blood pressure rises above normal, both decrease to reduce blood pressure.

Fluid Shifts

A decrease in plasma volume can temporarily be compensated for by a shift of the fluids out of the interstitial compartment to the plasma. The opposite is also true, an increase in plasma volume can cause fluid to shift to the interstitial compartment.

Long-term Control Factors

Fluid Input/Output

The short-term control mechanisms are only temporary and can only compensate for fairly minor changes in ECF volumes. Long-term regulation of blood pressure is a primary function of the kidneys and the thirst mechanism, controlling fluid output and input, respectively. Control of urine output by the kidneys is critical for long-term regulation of blood pressure.

STUDY TIPS & TOOLS

Come back to this slide to test your understanding of the short and long term mechanisms that control EFC.

Definition*:

Cardiac Output: The amount of blood pumped by the heart per minute.

Total Peripheral Resistance: This is the resistance to blood flow due to the constriction of blood vessels. Higher total peripheral resistance leads to increased blood pressure.

CONTROL OF SALT

This content was retrieved from Section 01, Slide 7 of 16 of the online learning module.

Sodium, and the anions that are associated with it (mainly chloride), account for more than 90% of the ECF's solutes. Whenever salt is transported across a membrane, water follows due to osmosis. Therefore, by controlling salt levels, ECF volume is being controlled.

To maintain salt balance, salt input must equal salt output.

Learn how salt balance is maintained through salt input and salt output.

Salt Input

Regulation of salt input is poor as it is dependent upon dietary salt. It is necessary on a daily basis to replace the salt lost in the feces and sweat, which is about 0.5g/day for normal activity levels (higher activity levels will increase the amount lost in sweat).

Compare this to the average input for Canadians of around 3.5 g/day.

Salt Output

The excess salt must be eliminated, which occurs in the kidneys. The three pathways to eliminate salt are in the feces, sweat, and the kidneys. As already mentioned, the kidneys have the greatest role in salt elimination. The precise control of how the kidneys regulate sodium excretion will be covered in detail in subsequent sections of this module.

Reference:

ixabay (n.d.) Scale. Retrieved January 2018 from <https://pixabay.com/en/photos/balance%20scale/>

QUESTION: CONTROL OF ECF OSMOLARITY

This content was retrieved from Section 01, Slide 8-9 of 16 of the online learning module.

Osmolarity is defined as a measure of the concentration of a particular solute in solution. A high osmolarity means that there is more solute, and therefore less water, in solution. Water moves down its concentration gradient until the osmotic pressure across a membrane is equalized. Because of this, regulating osmolarity is very important in preventing changes in cell volume.

Take a situation where there is a decrease in water in the ECF. This causes the osmolarity to increase and the ECF is what we call **hypertonic***. Since there is normally a balance in the osmolarity of the ICF and ECF, hypertonicity of the ECF causes water to move out of the cells into the ECF until the osmotic pressure is equalized. This loss of water from cells can cause them to shrink.

Using this knowledge, what do you think would occur if there was an increase in water in the ECF?

Feedback:

If there were an increase in water in the ECF, the osmolarity would decrease and the ECF would become hypotonic, meaning it would have a lower osmotic pressure than the surrounding cells. This would result in water moving into the cells until the osmotic pressures were equalized. This movement of water into the cells would cause them to expand.

If the ECF were very hypotonic, the amount of water moving into cells would cause them to burst.

As already mentioned, the cellular consequence of hypotonic ECF is the swelling, which impairs cellular function.

Definition*:

Hypertonic: A hypertonic solution is one in which the concentration of solutes within that solution is greater than that of another solution that is separated by a membrane.

HYPOTONICITY

This content was retrieved from Section 01, Slide 10 of 16 of the online learning module.

Hypotonicity of the ECF is usually associated with overhydration, or excess free H₂O, and has three major causes.

Learn about these causes.

Renal Failure

These individuals are not able to produce a concentrated urine.

Rapid Water Ingestion

This can occur in healthy individuals if they drink volumes of water in excess of what the kidneys can deal with in a timely manner.

Over Secretion of Vasopressin

Vasopressin promotes water retention.

Therefore, the osmolarity of the ECF must be regulated to prevent these undesirable shifts of H₂O into or out of cells. How does the extracellular fluid become hypertonic or hypotonic? We will explore this on the following slides.

CLINICAL APPLICATION

When renal failure occurs, dialysis is often the chosen treatment.

Learn how [*dialysis can keep a patient's body in balance during renal failure.*](#)

Page Link:

<https://www.kidney.org/atoz/content/dialysisinfo>

QUESTION: HYPERTONICITY

This content was retrieved from Section 01, Slide 11-12 of 16 of the online learning module.

Hypertonicity of the ECF, the excessive concentration of ECF solutes, is usually associated with dehydration and has three major causes.

Using what you have learned thus far in the course as well as past experience, come up with a few causes for hypertonicity.

Feedback:

1. *Insufficient water intake, or not drinking enough.*
2. *Diabetes insipidus, which involves a deficiency in vasopressin.*
3. *Excessive water loss due to heavy sweating during extreme exercise, prolonged bouts of vomiting, or diarrhoea.*

The cellular consequences of hypertonicity generally relate to a decrease of normal cell function as the ICF is decreased. The brain is particularly sensitive and shrinking of neurons can cause confusion, delirium, and even coma or death.

QUESTION: ISOTONIC FLUIDS

This content was retrieved from Section 01, Slide 13-14 of 16 of the online learning module.

Suppose that a patient with a normal osmotic balance is given a therapeutic intravenous administration of an isotonic solution.

Using what you have learned thus far, answer the following questions:

1. *What do you think is meant by **isotonic**?*
2. *Into what body water compartment is the solution being injected?*

3. What will be the effect on the volume and concentration of solutes in this compartment, and how do you predict this would impact cells?
4. How do you think isotonic fluid loss, such as haemorrhage, would impact cells?

Feedback:

An isotonic solution has an equal osmolarity to that of normal body fluids. In this case, the saline solution is being injected into the blood plasma within the veins, which makes up approximately one fifth of the ECF. When isotonic fluid is injected into the ECF compartment, ECF volume increases, but the concentration of ECF solutes remain unchanged; the ECF remains isotonic. Since the ECF osmolarity has not changed, the ECF and ICF are still in osmotic equilibrium, and there is no net fluid shift between the two compartments. Cells would neither shrink nor swell, illustrating the need for intravenous fluid therapy to be isotonic in order to prevent fluctuations of intracellular volume.

Similarly, in isotonic fluid loss, the loss is confined to the ECF, with no corresponding loss of fluid from the ICF. No osmotic gradient is created that would result in net fluid shifts.

REGULATION OF WATER BALANCE

This content was retrieved from Section 01, Slide 15 of 16 of the online learning module.

You have already learned the importance of maintaining water balance within the body for the proper functioning of cells. Within the hypothalamus, near the vasopressin-secreting cells and thirst centre, are hypothalamic osmoreceptors which constantly monitor the osmolarity of the fluid surrounding them in order to quickly counteract any fluctuations in water balance.

Learn about the regulation of water balance within the body.

1. Within the hypothalamus, near the vasopressin-secreting cells and thirst centre, are hypothalamic osmoreceptors which constantly monitor the osmolarity of the fluid surrounding them. As osmolarity increases, both vasopressin secretion and thirst are stimulated.
2. The vasopressin acts on the kidneys to increase water reabsorption, while thirst stimulates the intake of water to the body through drinking. This continues until the hypertonicity is relieved. If the fluid around the osmoreceptors is hypotonic, then vasopressin secretion and thirst are not stimulated, promoting water loss.
3. Large losses of ECF volume can also impact these pathways. Within the left atrium of the heart are what are called left atrial volume receptors, which monitor the pressure of the blood in the left atrium. They are activated when there is a greater than 7% loss of ECF volume and blood pressure. Once activated, they also stimulate the hypothalamic pathways to stimulate vasopressin release and thirst.

We will learn more about the details of these pathways as we examine kidney function.

QUESTION: SHORT-TERM VS. LONG-TERM CONTROL OF THE ECF VOLUME

This content was retrieved from Section 01, Slide 16 of 16 of the online learning module.

Select whether the following measures act in the short term and/or long term to adjust blood pressure through control of the ECF.

Baroreceptor reflex:	Short-term Control	Long-term Control
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The kidneys' control of urine output:	Short-term Control	Long-term Control
Fluid shifts in / out of the interstitial compartment:	Short-term Control	Long-term Control
The body's control of the thirst mechanism:	Short-term Control	Long-term Control
A change in cardiac output and total peripheral resistance:	Short-term Control	Long-term Control

Feedback:

Baroreceptor reflex:	Short-term Control	
The kidneys' control of urine output:		Long-term Control
Fluid shifts in / out of the interstitial compartment:	Short-term Control	
The body's control of the thirst mechanism:		Long-term Control
A change in cardiac output and total peripheral resistance:	Short-term Control	

SECTION 02: OVERVIEW OF THE KIDNEYS

SECTION 02: OVERVIEW OF THE KIDNEYS

This content was retrieved from Section 02, Slide 1 of 11 of the online learning module.

By the end of Section 02, you should be able to:

1. Describe the roles of the kidneys.
2. Describe the major structural components of a nephron.
3. Describe the basic renal processes involved in urine excretion.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 13: Pages 559-566

THE KIDNEYS

This content was retrieved from Section 02, Slide 2 of 11 of the online learning module.

The kidneys are controlled by both neural and endocrine inputs. The primary function of the kidneys are to maintain the ECF volume, electrolyte composition, and osmolarity.

In the presence of excess water or of a particular electrolyte (solute), the kidneys will increase their elimination. When there is a deficit of water or of a solute, the kidneys cannot actively correct this. However, they can further reduce their elimination.

The kidneys possess many major functions.

Review these functions.

1. Maintain water balance in the body
2. Maintain body fluid osmolarity
3. Maintain proper plasma volume
4. Help maintain acid-base balance
5. Regulate ECF solutes (such as sodium, potassium, chloride, calcium, phosphate, and others)
6. Excrete wastes of metabolism
7. Excrete foreign compounds ingested
8. Produce erythropoietin
9. Produce renin
10. Activate vitamin D

These functions will be explored throughout the remainder of the module.

KIDNEY STRUCTURE

This content was retrieved from Section 02, Slide 3 of 11 of the online learning module.

The kidneys are bean-shaped organs, each about 10 cm in length. Associated with each kidney is an adrenal gland, which is situated on top of the kidney. The outside of the kidney is the renal cortex and the inner part is called the renal medulla. At the inner core of each kidney is the renal pelvis, through which the urine empties and is channeled to the ureter.

The functional unit of the kidney is the **nephron**, of which there are more than one million in a healthy adult kidney. It is within the nephrons that blood is filtered to produce urine and the reabsorption of necessary fluids and molecules occurs.

Switch between images of the urinary system, kidney and nephron.

Note: You will learn about these structures in this section of the module.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE NEPHRON

This content was retrieved from Section 02, Slide 4 of 11 of the online learning module.

The nephron can be divided into two components.

The first component is the **vascular component**, which supplies blood to the nephron.

The second component is the **tubular component**, which carries the filtrate throughout the nephron.

Learn about each of the components.

The Vascular Component - Refer to pages 18-19

The Tubular Component - Refer to page 19

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE VASCULAR COMPONENT

Subpage of Section 02, Slide 4 of 11 – The Vascular Component - 1/1

The major part of the vascular component of the nephron is the **glomerulus**, which is a ball-like capillary through which water and solutes are filtered from the plasma. When blood enters the kidney via the renal artery, the **renal artery** subdivides into many small **afferent arterioles**, each of which supplies a nephron. Leaving the nephron are the efferent arterioles, which transport unfiltered blood from the glomerulus.

The capillaries of the nephron are different in that arterial blood enters and then leaves, with no oxygen extracted. Instead, the efferent arteries subdivide into capillaries, the **peritubular capillaries**, that deliver oxygen to the renal tissues.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE TUBULAR COMPONENT

Subpage of Section 02, Slide 4 of 11 – The Tubular Component - 1/1

Filtered blood enters a hollow tube, formed by a single layer of epithelial cells, that transports urine to the renal pelvis. Even though it is technically one long continuous tube, it is divided along its length based on differences in structure and function.

It begins with **Bowman's capsule**, which encircles the glomerulus to collect the fluid filtered from the glomerular capillaries. Fluid then passes into the **proximal tubule** within the renal cortex, which is highly coiled along its length. Next is the **loop of Henle**, which forms a hairpin loop that dips down into the renal medulla. The descending limb of the loop of Henle travels from the cortex to the medulla while the ascending limb travels from the medulla back to the cortex. The ascending limb passes through the fork of the afferent and efferent arteries in a region called the **juxtaglomerular apparatus**. The tubule now coils again and is called the **distal tubule**, also entirely within the cortex. The distal tubule empties into a **collecting duct**, which travels deep into the medulla and ultimately drains into the **renal pelvis**.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

TYPES OF NEPHRONS

This content was retrieved from Section 02, Slide 5 of 11 of the online learning module.

There are two types of nephrons.

Learn about these various structures.

Cortical Nephrons

The glomeruli of this type of nephron lie in the outer layer of the cortex. About 80% of all nephrons are cortical nephrons that primarily serve secretory and regulatory functions. Their loop of Henle only slightly dips into the renal medulla. The peritubular capillaries from this type of nephron wrap around the short loops of Henle.

Juxtamedullary Nephrons

This type of nephron is found on the inner layer of the cortex and are responsible for the concentration and dilution of urine. The peritubular capillaries from these nephrons form hairpin loops of vasculature, called the **vasa recta**, that are in close proximity to the long loops of Henle.

Note: the nephrons in this image are grossly exaggerated in size.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: THE FLOW OF BLOOD THROUGH THE NEPHRON

This content was retrieved from Section 02, Slide 6-7 of 11 of the online learning module.

Using what you have learned thus far about the nephron, select the correct terms from the drop-down list in order by which blood flows from the renal artery to the renal vein in the nephron.

Word Bin: Afferent Arteriole, Efferent Arteriole, Glomerulus, Peritubular Capillaries, Renal Artery, Renal Vein

1. ?
2. ?
3. ?
4. ?
5. ?
6. ?

Feedback:

1. Renal Artery
2. Afferent Arteriole
3. Glomerulus
4. Efferent Arteriole
5. Peritubular Capillaries
6. Renal Vein

THE BASIC RENAL PROCESSES

This content was retrieved from Section 02, Slide 8 of 11 of the online learning module.

When it comes to the formation of urine, there are three basic processes of the kidneys.

Learn about each process.

Glomerular Filtration (GF)

About 20% of the blood that flows through the glomerular capillaries is filtered into Bowman's capsule. It is important to note that this plasma filtrate is normally protein free, but does contain the same solutes as the plasma. Collectively, about 125 ml of glomerular filtrate is formed each minute.

Tubular Reabsorption (TR)

As the filtrate flows through the tubules, important substances are returned to the peritubular capillaries by the process of tubular reabsorption. Of the 180 litres of plasma filtered each day, about 178.5 is reabsorbed.

Tubular Secretion (TS)

This is the second route for substances in the blood to enter the renal tubules. Tubular secretion is the selective transfer of substances from the peritubular capillaries into the tubules. Remember, only 20% of the plasma is filtered in the glomeruli so this route allows excretion of selected substances from the remaining 80% of the plasma.

STUDY TIPS & TOOLS

Remember that the body reabsorbs “good” substances and secretes “bad” substances. Here is a phrase to help you remember this difference: Bad Studies Get Rejected!

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: ROLES AND FUNCTIONS OF THE KIDNEY

This content was retrieved from Section 02, Slide 9-10 of 11 of the online learning module.

Recall what you have learned about the roles of the kidney in the body.

In the box, try to list the 5 main functions of the kidney.

Feedback:

1. *Maintain water balance in the body*
2. *Maintain body fluid osmolarity*
3. *Regulate ECF solutes (such as sodium, potassium, chloride, calcium, phosphate, and others)*
4. *Maintain proper plasma volume*
5. *Excrete wastes of metabolism*

The kidney has 5 other main functions, most of which we will discuss in greater detail later in this module. These are to 1) Excreting foreign compounds ingested, 2) Producing erythropoietin, 3) Producing renin, 4) The activation of vitamin D, and 5) Helping to maintain the body's acid-base balance.

QUESTION: COMPARING TYPES OF NEPHRONS

This content was retrieved from Section 02, Slide 11 of 11 of the online learning module.

Select whether the listed statement is a characteristic of the cortical nephron or juxtamedullary nephron.

Characteristic:

- Lies in outer layer of cortex
- Mainly responsible for urine concentration/dilution
- Vasa recta are in proximity to the long loops of Henle
- Primarily serve secretory and regulatory functions
- About 80% of all nephrons
- Lie within inner layer of cortex
- Peritubular capillaries form hairpin loops of vasculature, called the vasa recta
- Loop of Henle only slightly dips into renal medulla

Feedback:

- Lies in outer layer of cortex - Cortical
- Mainly responsible for urine concentration/dilution - Juxtamedullary
- Vasa recta are in proximity to the long loops of Henle - Juxtamedullary

- Primarily serve secretory and regulatory functions - Cortical
- About 80% of all nephrons - Cortical
- Lie within inner layer of cortex - Juxtamedullary
- Peritubular capillaries form hairpin loops of vasculature, called the vasa recta - Juxtamedullary
- Loop of Henle only slightly dips into renal medulla - Cortical

SECTION 03: GLOMERULAR FILTRATION

SECTION 03: GLOMERULAR FILTRATION

This content was retrieved from Section 03, Slide 1 of 16 of the online learning module.

By the end of Section 03, you should be able to:

1. Describe the forces that regulate glomerular filtration.
2. Describe how glomerular filtration is regulated by the body, both intrinsically and extrinsically.
3. Explain why the kidneys receive a greater proportion of cardiac output, relative to its weight.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 13: Pages 566-573

THE GLOMERULUS

This content was retrieved from Section 03, Slide 2 of 16 of the online learning module.

The **glomerulus** is a network of capillaries located at the beginning of a nephron. Blood is filtered across the walls of this capillary network through the glomerular membrane, which yields its filtrate into **Bowman's capsule**. The filtrate then enters the renal tubule of the nephron.

The glomerulus receives its blood supply from an **afferent arteriole** and the glomerular capillaries exit into **efferent arterioles**. Three main forces are responsible for enabling glomerular filtration, as you will learn in this section.

The rate at which blood is filtered through all of the glomeruli, the measure of the overall renal function, is the **glomerular filtration rate (GFR)**.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

GLOMERULAR FILTRATION

This content was retrieved from Section 03, Slide 3 of 16 of the online learning module.

In order for blood to be filtered, the fluid must pass through three layers that make up the glomerular membrane.

Learn about these layers.

1. **The glomerular capillary wall.** Like most capillaries, it consists of a single layer of endothelial cells. However, it contains many large pores that make it 100 times more permeable to fluids and solutes than regular capillaries. The pores are of such size that large plasma proteins cannot pass through, but smaller ones, such as albumin, can.

2. **The basement membrane.** This layer contains no cells and is composed of collagen to provide structural strength, and glycoproteins to discourage the filtration of small plasma proteins. Because the glycoproteins are negatively charged, they help to repel any proteins that do get through the capillary walls. Only about 1% of filtered albumin will pass into Bowman's capsule.
3. **The inner layer of Bowman's capsule.** This layer is composed of **podocytes*** that form narrow filtration slits between them that allow fluid to pass into Bowman's capsule.

Definition*:

Podocytes: These are cells that wrap around the capillaries of the glomerulus.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

FORCES THAT REGULATE GLOMERULAR FILTRATION

This content was retrieved from Section 03, Slide 4 of 16 of the online learning module.

The forces involved in glomerular filtration are very conceptually similar to the forces involved in bulk flow across any capillary wall that you learned in Module 06.

Learn about the three physical forces involved.

Glomerular Capillary Blood Pressure

This is the pressure exerted by the blood in the glomerular capillaries. While regular capillaries have a blood pressure of about 18 mmHg, glomerular capillary pressure is on average **55 mmHg**. This is due mainly to the afferent arteriole diameter being larger than the diameter of the efferent arterioles, which increases resistance to blood leaving the glomerular capillaries. This also prevents glomerular capillary pressure from decreasing along their length, further favouring filtration.

Plasma-Colloid Oncotic Pressure

The presence of large proteins in the plasma that cannot be filtered produces an oncotic force that resists the movement of water into Bowman's capsule. The plasma-colloid oncotic pressure is about **30 mmHg**.

This image demonstrates Bowman's capsule and the glomerular capillaries.

Bowman's Capsule Hydrostatic Pressure

This is the pressure of the fluid in Bowman's capsule and it also resists the movement of water out of the glomerular capillaries. Bowman's capsule hydrostatic pressure is around **15 mmHg**.

This image demonstrates Bowman's capsule and the glomerular capillaries.

Therefore, net filtration pressure equals the glomerular capillary blood pressure minus the sum of the plasma-colloid oncotic and Bowman's capsule hydrostatic pressures.

Net Filtration Pressure = 55 mmHg - (30 mmHg + 15 mmHg) = **10 mmHg**

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

GLOMERULAR FILTRATION RATE

This content was retrieved from Section 03, Slide 5 of 16 of the online learning module.

So far we have talked about the pressures involved in glomerular filtration. We will now talk about **glomerular filtration rate (GFR)** and how it is regulated. GFR is not only dependent upon filtration pressure, but also the glomerular surface area available and how permeable the membrane is.

Collectively, these properties are called the **filtration coefficient (K_f)**.

We can now mathematically express GFR as:

Filtration Coefficient (K_f) x Filtration Pressure = Glomerular Filtration Rate

In the average male, this value is 125 ml/min, and in females it is 115 ml/min!

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: UNCONTROLLED INFLUENCES ON GFR

This content was retrieved from Section 03, Slide 6-7 of 16 of the online learning module.

Normally plasma-colloid osmotic pressure and Bowman's capsule hydrostatic pressure do not vary much and are essentially considered constants. However, both of these values can change due to pathological conditions.

Review an example of a pathological condition that leads to changes in GFR.

Someone with a kidney stone that obstructs the ureter will have an increased Bowman's capsule hydrostatic pressure, again decreasing GFR.

Using what you know now about how GRF can be decreased, and the example about kidney stones, think of another way by which GRF could be decreased.

Feedback:

Although you may have come up with another possible example, our example is in the case of diarrhea. Someone with severe diarrhea will be dehydrated, as they are losing more fluid than they are taking in. This results in decreased blood pressure due to the decreased plasma volume. There is also an increase in plasma-colloid osmotic pressure that results in a decreased GFR.

References:

N I H. (2017). Definition & Facts for Kidney Stones. National Institute of Diabetes and Digestive and Kidney Diseases. Retrieved November 2017 from: https://www.news-medical.net/image.axd?picture=2017%2F9%2Fshutterstock_409736524.jpg

Coles, T. (2016). Everything you need to know about diarrhea. Huffington Post. Retrieved January 2018 from: <http://www.mixedmash.com/wp-content/uploads/2017/08/o-DIARRHEA-570.jpg>

CONTROLLED CHANGES IN THE GFR

This content was retrieved from Section 03, Slide 8 of 16 of the online learning module.

Review the equations.

Recall the following equation used to determine net filtration pressure:

1. Glomerular Capillary Blood Pressure - (Plasma-colloid Oncotic Pressure + Bowman's Capsule Hydrostatic Pressure) = Net Filtration Pressure

Even though plasma-colloid osmotic pressure and Bowman's capsule hydrostatic pressure generally do not change, glomerular capillary blood pressure can be regulated.

Recall the following equation used to determine glomerular filtration rate:

2. Filtration Coefficient (K_f) x Net Filtration Pressure = Glomerular Filtration Rate (GFR)

As you can see from these two equations, changes in GFR are proportional to changes in glomerular capillary blood pressure.

AUTOREGULATION

This content was retrieved from Section 03, Slide 9 of 16 of the online learning module.

Because changes in GFR are directly proportional to glomerular capillary blood pressure, autoregulatory (or intrinsic) mechanisms are in place to prevent sudden swings in GFR.

This is primarily done by regulating the diameter of the afferent arterioles, such that constricting the afferent arterioles will decrease glomerular capillary blood pressure and dilating the afferent arterioles will increase it.

There are two intrarenal mechanisms that allow this to happen.

Learn about these mechanisms.

Myogenic Activity - Refer to pages 26-27

Tubuloglomerular Feedback (TGF) - Refer to page 27

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

MYOGENIC ACTIVITY

Subpage of Section 03, Slide 9 of 16 - Myogenic Activity - 1/1

This is the same myogenic response that we talked about for smooth muscle in vascular walls. When an increased pressure stretches the afferent arteriole walls, they automatically constrict to reduce blood flow to the glomerular capillaries and thus prevent an increase in GFR.

The opposite is also true in that if blood pressure decreases, the afferent arterioles will dilate to increase blood flow and prevent a decrease in GFR.

Note that the constriction of blood vessels is known as vasoconstriction, and that vasodilation is the dilation of blood vessels.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

TUBULOGLOMERULAR FEEDBACK (RGF)

Subpage of Section 03, Slide 9 of 16 – Tubuloglomerular Feedback (TGF) - 1/1

Recall that the juxtaglomerular apparatus is the area of the distal tubule that passes through the region where the afferent and efferent arterioles join the glomerulus. It is a combination of vascular and tubular cells.

Specialized tubular cells in this area are collectively called the **macula densa**, which can sense changes in the salt level of the tubular fluid. If there is an increased arterial pressure that increases the GFR, more fluid than normal will flow through the distal tubule. This also means there is an increased salt delivery. In response, the macula densa releases ATP, which is degraded to adenosine. This adenosine acts on the afferent arterioles to cause constriction and reduce GFR. The opposite is also true.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: AUTOREGULATION OF GFR

This content was retrieved from Section 03, Slide 10-11 of 16 of the online learning module.

Using what you have learned thus far about the autoregulation of GFR, discuss what you believe would occur to the glomerular capillary blood pressure, net filtration pressure, and the glomerular filtration rate if there was vasoconstriction in the afferent arteriole? What would occur if there was vasodilation of the afferent arteriole? Explain your reasoning.

Feedback:

Recall that net filtration pressure is proportional to the glomerular capillary pressure, as both the plasma-colloid oncotic and Bowman's capsule hydrostatic pressures are nearly constant. Also recall that the glomerular filtration rate (GFR) is equal to the filtration pressure multiplied by the filtration coefficient. Therefore, any change in glomerular capillary pressure is proportionally reflected in both the filtration pressure and glomerular filtration rate.

In the case of vasoconstriction of the afferent arteriole, there would be a decrease in glomerular capillary blood pressure, a decrease in net filtration pressure, and a decrease in glomerular filtration rate.

In the case of vasodilation of the afferent arteriole, there would be an increase in glomerular capillary blood pressure, an increase in net filtration pressure, and an increase in glomerular filtration rate.

SYMPATHETIC CONTROL OF GFR

This content was retrieved from Section 03, Slide 12 of 16 of the online learning module.

In addition to intrinsic controls, GFR is also under extrinsic control, independent of fluctuations in arterial blood pressure. This is controlled by the sympathetic nervous system, which innervates the afferent arterioles.

Let's use a haemorrhage as an example (i.e. a sudden loss of blood volume followed by a drop in arterial pressure). This would be sensed by the **baroreceptors***, which would initiate responses to normalize blood pressure.

At the level of the kidney, this increased sympathetic activity would constrict the afferent arterioles, which would decrease glomerular capillary pressure, decreasing GFR, and reducing urine production. This is a mechanism by which depleted plasma volumes can be corrected.

Definition*:

Baroreceptors: Mechanoreceptors that detect changes in blood pressure.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE KIDNEYS AND CARDIAC OUTPUT

This content was retrieved from Section 03, Slide 13 of 16 of the online learning module.

In a healthy person, about 20% of the plasma enters the kidneys and becomes the glomerular filtrate. This means that if $GFR = 125 \text{ ml/minute}$, the total blood flow to the kidneys must be 5×125 or 625 ml/minute .

Additionally, considering that only 55% of whole blood is filterable plasma, we can adjust renal blood flow to 1140 ml/minute . Since total cardiac output equals around 5000 ml/minute at rest, we can now calculate that the kidneys receive around 22% of the total cardiac output. This proportion far exceeds what would be expected based on tissue size since kidney weight is only about 1% of total body weight.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: WHY IS CARDIAC OUTPUT SO HIGH?

This content was retrieved from Section 03, Slide 14-15 of 16 of the online learning module.

What do you think is the functional significance of the kidneys receiving such a high proportion of total cardiac output?

Feedback:

This large proportion of cardiac output signifies the importance of the kidneys! Its primary purpose is not to deliver oxygen and nutrients, but rather to deliver blood for "cleaning". Delivery of this large volume of blood also allows the kidneys to maintain tight control of volume and electrolyte concentrations of the body's water pools and to eliminate wastes efficiently.

Reference:

Can Stock Photo (n.d.) Kidneys. Retrieved January 2018
from https://cdn.xl.thumbs.canstockphoto.com/vector-kidneys-illustration-vector-clip-art_csp25438512.jpg

QUESTION: SYMPATHETIC CONTROL OF GFR

This content was retrieved from Section 03, Slide 16 of 16 of the online learning module.

Select the "Action" from the drop down list to predict the sequential actions of the body in response to decreased arterial blood pressure.

Word Bin: Decrease in Glomerular Capillary Blood Pressure, Generalized Arteriolar Vasoconstriction, Increase in Sympathetic Activity, Increase in Conservation of Fluid and Salt

3. ↓ Arterial Blood Pressure
4. Detection by aortic arch and carotid sinus baroreceptors?
5. ?
6. ?
7. Afferent Arteriolar Vasoconstriction
8. ?
9. ↓ GFR
10. ↓ Urine Volume
11. ?
12. ↑ Arterial Blood Pressure

Feedback:

1. ↓ Arterial Blood Pressure
2. Detection by aortic arch and carotid sinus baroreceptors?
3. **Increase in Sympathetic Activity**
4. **Generalized Arteriolar Vasoconstriction**
5. Afferent Arteriolar Vasoconstriction
6. **Decrease in Glomerular Capillary Blood Pressure**
7. ↓ GFR
8. ↓ Urine Volume
9. **Increase in Conservation of Fluid and Salt**
10. ↑ Arterial Blood Pressure

SECTION 04: TUBULAR REABSORPTION

SECTION 04: TUBULAR REABSORPTION

This content was retrieved from Section 04, Slide 1 of 22 of the online learning module.

By the end of Section 04, you should be able to:

1. Describe the process of transepithelial transport using sodium as an example.
2. Describe how the reabsorption of sodium is regulated.
3. Define T_m and explain why it is important in the reabsorption of necessary substances.
4. Describe the reabsorption of water along the entire tubule.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 13: Pages 573-582

TUBULAR REABSORPTION (2)

This content was retrieved from Section 04, Slide 2 of 22 of the online learning module.

The glomerular filtrate that enters the tubules is identical to plasma with the exception of plasma proteins. That is, there is no selectivity to glomerular filtration. Tubular reabsorption includes the processes by which water and other necessary solutes are returned to the plasma, while allowing waste products to remain in the filtrate.

Reabsorption is a two step process.

Review this process.

1. Reabsorption begins with either active or passive movement of substances from the tubule into the interstitial space.
2. Reabsorption then continues with passive movement of substances from the interstitial space back into the bloodstream.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE FATE OF VARIOUS SUBSTANCES FILTERED BY THE KIDNEYS

This content was retrieved from Section 04, Slide 3 of 22 of the online learning module.

Unlike glomerular filtration, tubular reabsorption is highly selective and variable.

In general, the tubules have a high reabsorptive capacity for substances needed by the body, and a low reabsorptive capacity for substances not needed by the body. Since water and solutes are critical for maintaining homeostasis, their tubular reabsorption is high.

This general trend can be seen in the table comparing the percentages of reabsorbed and excreted substances.

Substance	Average Percentage of Filtered Substance Reabsorbed	Average Percentage of Filtered Substance Excreted
Water	99	1
Sodium	99.5	0.5
Glucose	100	0
Urea (a waste product)	50	50
Phenol (a waste product)	0	100

Note: You do not need to memorize these numbers. Focus on understanding the trends.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

TRANSEPITHELIAL TRANSPORT

This content was retrieved from Section 04, Slide 4 of 22 of the online learning module.

As already mentioned, the tubule is composed of a single layer of epithelial cells. The area of the epithelial cells that are in contact with the tubule lumen is the **luminal membrane**, and the area of the epithelial cells that are in contact with the interstitial fluid is the **basolateral membrane**.

Transepithelial transport (sometimes called transcellular transport) is defined as the movement of solutes across an epithelial cell layer through the cell.

The membranes from neighbouring epithelial cells are not in contact, other than where there are tight junctions connecting them. Because of this, any substance that enters an epithelial cell cannot transport it to a neighbouring cell, the substance must move through the cell into the interstitial space.

The membranes from neighbouring epithelial cells are not in contact, other than where there are tight junctions connecting them. Because of this, any substance that enters an epithelial cell cannot transport it to a neighbouring cell, the substance must move through the cell into the interstitial space.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

THE STEPS OF TRANSEPITHELIAL TRANSPORT

This content was retrieved from Section 04, Slide 5 of 22 of the online learning module.

There are essentially five steps that must occur for transepithelial transport.

Learn about five steps involved in transepithelial transport.

1. The substance must cross the luminal membrane.

2. The substance must pass through the cytosol.
3. The substance must cross the basolateral membrane.
4. It must diffuse through the interstitial fluid.
5. It must cross the capillary wall to enter the plasma.

It is important to note that this transport can be both passive and active. Rather than specifically describe the absorptive process for each of the filtered substances returned to the plasma, we will discuss the general mechanisms involved in the important case of Na^+ reabsorption.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

LOCATIONS OF Na^+ REABSORPTION

This content was retrieved from Section 04, Slide 6 of 22 of the online learning module.

As you can imagine, since 99.5% of all filtered Na^+ is reabsorbed, this process is highly controlled. Unlike most solutes, Na^+ can be reabsorbed to various extents along the entire tubule. The reason why Na^+ is reabsorbed in so many places is that it is critical to the reabsorption of many other substances.

Learn about the different locations of Na^+ reabsorption within the kidney.

The proximal tubule

In the proximal tubule, 76% of Na^+ is reabsorbed. Reabsorption of Na^+ in this segment of the nephron is needed for the reabsorption of glucose, amino acids, water, Cl^- , and urea.

The ascending limb of the loop of Henle

The loop of Henle absorbs 25% of the total reabsorbed Na^+ . In the ascending limb of the loop of Henle, Na^+ along with Cl^- are essential to either concentrate, or dilute, the urine depending upon the body's needs.

The distal and collecting tubules

The distal and collecting tubules collectively reabsorb 8% Na^+ . It is here that Na^+ reabsorption is under hormonal control and plays a key role in regulating ECF volume and secretion of both K^+ and H^+ .

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

ACTIVE TRANSPORT OF Na^+

This content was retrieved from Section 04, Slide 7 of 22 of the online learning module.

The reabsorption of Na^+ is both active and passive. Na^+ moves passively across the luminal membrane, but the movement of Na^+ across the basolateral membrane is by active transport involving the **Na^+-K^+ ATPase pump**.

Due to the large volume of Na^+ that is reabsorbed, its transport accounts for 80% of the energy needs of the kidney. By actively transporting Na^+ into the interstitial fluid, it helps to keep the cytosol Na^+ concentration low to allow for the passive diffusion across the luminal membrane.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

PASSIVE TRANSPORT OF Na^+

This content was retrieved from Section 04, Slide 8 of 22 of the online learning module.

The mechanism of passive transport of Na^+ across the luminal membrane varies throughout the various segments of the tubule.

In the proximal tubule, Na^+ crosses by a cotransport carrier that simultaneously moves organic nutrients, such as glucose and amino acids. These nutrients are transferred by secondary active transport, as they use the concentration gradient of Na^+ established by the $\text{Na}^+\text{-K}^+$ ATPase pump to be transported against their concentration gradient, along with the passive transport of Na^+ .

In contrast, in the collecting duct, Na^+ passively enters the epithelial cells through a Na^+ channel.

Note that though this image only shows the transport of glucose, the transport of amino acids is identical to that of glucose.

Reference:

Slide Player (n.d.) Kidney Transport Reabsorption of filtered water and solutes from the tubular lumen across the tubular epithelial cells, through the renal interstitium. Retrieved January 2018 from <http://slideplayer.com/slide/4335325/>

QUESTION: TRANSEPITHELIAL TRANSPORT

This content was retrieved from Section 04, Slide 9 of 22 of the online learning module.

Before we continue in our discussion of the reabsorption of Na^+ and other substances, let us review the fundamental steps of transepithelial transport.

For a substance moving from the tubular membrane to the peritubular capillary, order the steps of transepithelial transport in the sequence in which they occur.

- The substance must cross the basolateral membrane
- The substance must cross the luminal membrane
- It must diffuse through the interstitial fluid
- It must cross the capillary wall to enter the plasma
- The substance must pass through the cytosol

Feedback:

1. The substance must cross the luminal membrane
2. The substance must pass through the cytosol

3. The substance must cross the basolateral membrane
4. It must diffuse through the interstitial fluid
5. It must cross the capillary wall to enter the plasma

HORMONAL REGULATION OF Na^+

This content was retrieved from Section 04, Slide 10 of 22 of the online learning module.

In the proximal tubule and the loop of Henle, a constant percentage of the filtered Na^+ is reabsorbed regardless of the total amount of Na^+ within the body fluids. In the distal tubule, however, the reabsorption of a small percentage of the filtered Na^+ is subject to hormonal control.

The most important, and most well-known, hormonal system involved in the regulation of Na^+ is the renin-angiotensin-aldosterone system (RAAS). Within the juxtaglomerular apparatus, there are granular cells that secrete renin into the blood.

Learn about the three primary triggers of renin secretion.

1. When the granular cells detect a drop in blood pressure, they secrete renin.
2. The granular cells are innervated by the sympathetic nervous system and will release renin when sympathetic activity increases.
3. The macula densa cells in the tubular portion of the juxtaglomerular apparatus are sensitive to the Na^+ and when there is a decrease in luminal Na^+ , the macula densa cells trigger the granular cells to secrete renin.

RENIN AND Na^+

This content was retrieved from Section 04, Slide 11 of 22 of the online learning module.

Once renin has been secreted into the blood, a series of events occur to regulate Na^+ within the blood.

Learn about the sequence of events involved in the RAAS system.

Renin

Once secreted, renin acts like an enzyme to convert **angiotensinogen*** into angiotensin I.

Angiotensin-converting enzyme

When circulating angiotensin I passes through the lungs, it is converted to angiotensin II by the enzyme angiotensin converting enzyme (ACE).

Angiotensin II

Angiotensin II, in turn, stimulates the adrenal cortex to release aldosterone.

Aldosterone

Aldosterone then causes an increase in Na^+ reabsorption in the distal and collecting tubules. You will learn the mechanism of this process on the next slide.

Definition*:

Angiotensinogen: A protein made in the liver that is present at high concentrations in the plasma.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

ACTIONS OF ALDOSTERONE

This content was retrieved from Section 04, Slide 12 of 22 of the online learning module.

Under the influence of aldosterone, tubular epithelial cells increase the insertion of Na⁺ channels in the luminal membrane and Na⁺-K⁺-ATPase carriers in the basolateral membrane.

Combined, this results in a greater passive flow of Na⁺ out of the tubular fluid.

This enhanced Na⁺ retention also causes increased water retention (remember that water follows Na⁺) and will therefore increase arterial blood pressure.

[Watch this video:](#) to gain an in depth understanding of the actions of aldosterone.

While watching, pay attention to the ways in which aldosterone can increase blood pressure.

Page Link:

<https://www.youtube.com/embed/yNiBtBro0dl>

Reference :

Aldosterone Mechanism of Action (Jul 15 2017) Youtube. Retrieved Jan 2018 from <https://www.youtube.com/embed/yNiBtBro0dl>

ATRIAL NATRIURETIC PEPTIDE (ANP)

This content was retrieved from Section 04, Slide 13 of 22 of the online learning module.

ANP is another hormone involved in the regulation of Na⁺ and water. Its actions, however, are opposite to those of aldosterone in that ANP release reduces Na⁺ load and blood pressure. When blood volume increases, or there is an increase in venous return, stretch receptors in the left atrium, aortic arch, and carotid sinus stimulate the release of ANP. It has three main actions.

Learn about these actions.

1. It directly inhibits Na⁺ reabsorption in the distal tubules so there is more Na⁺ excreted in the urine.
2. It inhibits both renin and aldosterone secretion.
3. It dilates the afferent arterioles and increases GFR. As more salt and water are filtered, more salt and water are excreted.

ACTIVELY REABSORBED SUBSTANCES

This content was retrieved from Section 04, Slide 14 of 22 of the online learning module.

So far we have focused on the reabsorption of Na^+ , however, many other substances are also transported across the tubule wall. Any substance that is actively reabsorbed will bind to a specific carrier protein in the plasma membrane. Because there are a limited number of carrier proteins in a membrane, there is a limit to how much of a substance can be reabsorbed. This is designated as the **tubular, or transport, maximum (T_m)**.

For any given substance, if its concentration in the tubular fluid exceed its T_m , then the excess will be excreted in the urine. The plasma concentration at which the T_m is exceeded is called the **renal threshold**. This is depicted in the graph, which we will explore further in upcoming slides.

The plasma concentration of many substances are essentially regulated by the kidneys and this carrier-mediated limitation. An example of this would be phosphate. In contrast, some substances, like glucose, have a T_m but their plasma concentrations are not regulated by the kidneys. We will look at these two examples in more detail.

Reference :

Chapter 18 - Urinary System: Renal Function. (n.d.) Retrieved January 2018
from http://droualb.faculty.mjc.edu/Course%20Materials/Physiology%20101/Chapter%20Notes/Fall%202011/chapter_18%20Fall%202011.htm

PHOSPHATE AND THE KIDNEYS

This content was retrieved from Section 04, Slide 15 of 22 of the online learning module.

For many electrolytes, such as phosphate and calcium, the kidneys help to regulate their plasma concentration. Let's use phosphate as an example.

Regulation of the plasma concentration of phosphate within the kidney is achieved because the renal threshold for phosphate is the same as the normal plasma concentration of phosphate. Since our diets are very rich in phosphate, after eating, there is a rise in the plasma concentration of phosphate. This increases the filtered load of phosphate but since the maximum for reabsorption is the same as the plasma phosphate concentration, all phosphate above the normal plasma concentration is excreted in the urine. This restores the plasma phosphate concentration to normal.

Unlike the reabsorption of organic nutrients like glucose and amino acids, the reabsorption of phosphate and calcium are under hormonal control. Hormones can alter their renal thresholds to modulate their reabsorption to match the body's needs.

Learn about situations in which this may occur. - Refer to pages 36-37

THE HORMONAL CONTROL OF PHOSPHATE

Subpage of Section 04, Slide 15 of 22 - Learn about situations in which this may occur - 1/1

Parathyroid hormone (PTH), as we discussed in Module 07, can alter the renal thresholds for phosphate and calcium and can adjust the quantity of conserved electrolytes, depending on the body's needs.

A fall in plasma concentration results in two effects which help raise the circulating level back to normal.

Learn about these two effects.

1. First, because of the inverse relationship between the phosphate and calcium concentrations in the plasma, a fall in plasma phosphate increases plasma calcium, which directly suppresses P T H secretion. In the presence of reduced P T H, phosphate reabsorption by the kidneys increases, returning plasma phosphate concentration toward normal.
2. Second, a fall in plasma also increases activation of vitamin D within the kidney, which then promotes absorption in the intestine.

GLUCOSE AND THE KIDNEYS

This content was retrieved from Section 04, Slide 16 of 22 of the online learning module.

As mentioned, glucose plasma concentrations are not regulated by the kidneys. The plasma concentration of glucose is normally 100 m g per 100 m l of plasma. Glucose is also small enough that it is freely filterable and the concentration in Bowman's capsule filtrate is the same as it is in the plasma. Given that the normal GFR is 125 m l/min, we can calculate that 125 mg/min glucose is filtered.

This is what is called the filtered load of a substance and is calculated as:

Filtered load = plasma concentration x GFR

Filtered load of glucose = 100 m g/100 m L x 125 m l/min = 125 m g/min

As seen in the graph, any increase in GFR results in a proportional increase in its filtered load.

How much glucose, however, is reabsorbed?

You will learn about the reabsorption of glucose in the next several slides.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: GLUCOSE AND THE KIDNEYS

This content was retrieved from Section 04, Slide 17-20 of 22 of the online learning module.

We have already mentioned that carrier mediated substances, like glucose, all have a T_m for reabsorption.

From what you have now learned about glucose and plasma concentrations in the kidney, at what plasma concentration will glucose start appearing in the urine? Refer to the graph for reference.

As you may know, diabetes mellitus causes increased glucose levels in the blood. This, in turn, can cause increased levels of glucose in the urine.

Using what you have learned thus far about the kidneys' ability to filter glucose, explain why this increase in glucose in the urine exists.

Feedback:

1) In the case of glucose, its normal T_m is 375 m g/min. This means that for all filtered loads of glucose below 375 m g/min, 100% of the glucose will be reabsorbed. Only when the filtered load of glucose exceeds 375 m g/min will glucose appear in the urine.

2) Ordinarily, urine contains no glucose because the kidneys are able to reabsorb it all. Bowman's capsule collects the filtrate that the glomerulus forms which includes urea, electrolytes, and glucose. The filtrate then passes into the proximal tubule to be reabsorbed. Proximal tubule, however, can only reabsorb a limited amount of glucose. When blood glucose levels exceed about 160-180 m g/100 m L, the proximal tubule is overwhelmed and begins to excrete glucose into the urine.

CHLORIDE, WATER, AND UREA

This content was retrieved from Section 04, Slide 21 of 22 of the online learning module.

Not only is the secondary active reabsorption of glucose and amino acids linked to the $\text{Na}^+\text{-K}^+$ ATPase pump, but the passive reabsorption of chloride, water, and urea also depends on this active Na^+ reabsorption mechanism.

Learn about how water, chloride and urea are reabsorbed by the body.

Water

Water is passively reabsorbed all along the tubule as it follows sodium. The following indicates how much water is reabsorbed at various locations within the kidney:

1. Proximal tubule - 65% (117 litres a day!)
2. Loop of Henle - 15%
3. Distal and collecting tubules - 20%

The fraction of water reabsorbed in the proximal tubule and loop of Henle is constant, despite the sodium and water load in the body. The proportion of water reabsorbed in the distal tubule and collecting tubule can vary depending on hormonal influences and the hydration state of the body.

Water flows through water channels called aquaporins. Those in the proximal tubule are always open allowing the flow of water by osmosis. Those in the distal tubule are under control by vasopressin, so they are not always open.

Sodium alone doesn't produce the osmotic driving forces to bring water from the tubules into the peritubular capillaries. The plasma-colloid oncotic pressure of the peritubular capillaries also produces a strong osmotic drive for water reabsorption.

Chloride

Despite the high concentration of chloride in the plasma, the kidneys do not directly regulate it. The majority of chloride does not undergo transepithelial transport, rather it leaves the tubular fluid by moving between the epithelial cells. It goes down its electrochemical gradient, essentially following the amount of Na^+ reabsorption. Therefore, the amount of chloride reabsorbed is determined by the amount of sodium reabsorbed.

Urea

Though urea is a waste product from the breakdown of protein, a large amount of urea is reabsorbed.

The concentration of urea at the beginning of the proximal tubule is the same as the plasma concentration of urea so there is no net diffusion. However, as fluid moves through the proximal tubule, its volume is reduced by 2/3 as water is reabsorbed so the tubular concentration of urea increases three-fold. Because of this, it passively is reabsorbed.

With each pass through the nephron, only 40-50% of plasma urea is filtered and excreted from the body. Blood urea, measured as blood urea nitrogen (B U N), has historically been used as a measure of renal failure. During renal failure, less urea is excreted so it accumulates in the plasma and can be clinically measured.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: RENIN AND THE REGULATION OF Na^+

This content was retrieved from Section 04, Slide 22 of 22 of the online learning module.

Now that you have an idea of how renin and Na^+ are regulated, drag and drop the correct responses to complete the chart.

Word Bin: Aldosterone, Angiotensin, Angiotensin converting enzyme (ACE), Angiotensin I

Feedback:

(Left or right): Angiotensin, Angiotensin I, Angiotensin converting enzyme (ACE), Aldosterone

SECTION 05: TUBULAR SECRETION

SECTION 05: TUBULAR SECRETION

This content was retrieved from Section 05, Slide 1 of 9 of the online learning module.

By the end of Section 05, you should be able to:

1. Describe the secretion of hydrogen and potassium ions.
2. Describe why it is necessary to secrete organic anions and cations.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 13: Pages 583-585

TUBULAR SECRETION (2)

This content was retrieved from Section 05, Slide 1 of 9 of the online learning module.

As you may have guessed, tubular secretion is the opposite of tubular reabsorption, though it also occurs via transepithelial transport. Tubular secretion involves the movement of substances from the peritubular capillaries to the tubule lumen, and thus is an additional pathway, other than glomerular filtration, for the removal of substances from the body.

Various substances undergo tubular secretion, the most important being hydrogen ions, potassium ions, and organic anions and cations, many of which are foreign to the body. We will now look at the details of the tubular secretion of each of these substances individually.

HYDROGEN ION SECRETION

This content was retrieved from Section 05, Slide 1 of 9 of the online learning module.

Hydrogen ions can be secreted in the **proximal**, **distal**, and **collecting tubules**. The extent to which they are secreted in the tubules depends on the acidity of the plasma.

When too much H⁺ is present in the plasma, more H⁺ undergoes tubular secretion. Conversely, when plasma H⁺ is low, tubular secretion of H⁺ decreases.

Renal H⁺ secretion plays a key role in the regulation of acid-base balance, which we will be looking at in greater detail in Module 05.

Reference:

My Biomedical Notebook. (2012). Renal Physiology, Fluid, and Electrolyte Balance. Retrieved January 2018 from: <http://2.bp.blogspot.com/-SXMQyjQ7Yok/UNcPFQIOmXI/AAAAAAAAAFU/nz3N98yNpkM/s1600/renal7.jpg>

POTASSIUM ION SECRETION

This content was retrieved from Section 05, Slide 1 of 9 of the online learning module.

Potassium ions actually undergo both tubular reabsorption and tubular secretion. Potassium is freely filtered at the glomerulus, but then actively reabsorbed in the proximal tubule.

The majority of the K^+ is reabsorbed in an unregulated fashion. However, its secretion is variable and subject to regulation. If the plasma concentration of K^+ is elevated, K^+ is actively secreted in the distal and collecting tubules, and vice versa. In this manner, the kidneys are actively involved in regulating plasma K^+ levels.

Potassium ion secretion in the distal and collecting tubules is an active process dependent upon the $Na^+ - K^+ -ATPase$ pump.

Remember when talking about Na^+ reabsorption, the Na^+ concentration gradient was maintained by pumping Na^+ out across the basolateral membrane in exchange for K^+ . Since most of the K^+ was reabsorbed in the proximal tubules, this makes a concentration gradient such that K^+ moves down its concentration gradient and passes through K^+ channels in the luminal membrane into the tubular fluid.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: POTASSIUM ION SECRETION

This content was retrieved from Section 05, Slide 5-6 of 9 of the online learning module.

Using what you have just learned about K^+ ion secretion into the lumen, answer the following question.

Since K^+ secretion is linked with Na^+ reabsorption by the $Na^+ - K^+ -ATPase$ pump, why isn't K^+ secreted throughout the Na^+ - reabsorbing segments of the tubule, instead of taking place only in the distal parts of the nephron?

Feedback:

The answer lies in the location of the passive K^+ channels. In the distal and collecting tubules, the K^+ channels through which K^+ passively diffuses are concentrated in the luminal membrane, providing a route for K^+ pumped into the cell to exit into the lumen, thus being secreted. However, in the reabsorbing tubular segments, these channels are located primarily in the basolateral membrane. As a result, K^+ pumped into the cell from the interstitial space simply moves back out into the interstitial space through these channels. This K^+ recycling permits the ongoing operation of the $Na^+ - K^+ -ATPase$ pump to accomplish reabsorption with no local net effect on K^+ .

CONTROL OF K^+ SECRETION

This content was retrieved from Section 05, Slide 7 of 9 of the online learning module.

Several factors can alter the rate of K^+ secretion.

Learn about the control of K^+ secretion.

Na⁺ and K⁺

A rise in plasma K⁺ directly stimulates the release of aldosterone from the adrenal cortex. As we discussed for regulation of Na⁺ reabsorption, aldosterone will increase Na⁺ reabsorption, which in turn means more K⁺ will be secreted. This relationship between Na⁺ reabsorption and K⁺ secretion means that stimuli such as a decreased plasma Na⁺, decreased ECF volume, or a decrease in arterial blood pressure can inadvertently stimulate abnormal K⁺ secretion to the extent that K⁺ depletion occurs.

Effect of H⁺ secretion

Another important factor that regulates K⁺ secretion is the acid-base status of the body. The Na⁺-K⁺-ATPase pump on the basolateral membrane of the distal sections of the nephron can readily substitute H⁺ for K⁺. Because there is a limited number of pumps, when the interstitial concentration of one of these ions increases, it can decrease the rate at which the other is transported. When the plasma is too acidic, H⁺ move into the interstitial space and are transported into the epithelial cell where they passively move into tubular fluid, as already discussed. The consequence is that less K⁺ is secreted, which can lead to an inappropriate high levels of K⁺.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

SECRETION OF ORGANIC ANIONS AND CATIONS

This content was retrieved from Section 05, Slide 8 of 9 of the online learning module.

The proximal tubule contains two types of secretory carriers, one for organic anions and another for organic cations.

These organic ion secretory systems are important for three main reasons.

Learn about these functions.

Increasing Excretion

Actively adding more organic ions to the tubular fluid, in addition to that which was filtered, can increase the amount of the organic ion excreted compared to glomerular filtration alone. This is particularly important for blood-borne chemical messengers such as norepinephrine, histamine, and prostaglandins in order to reduce or limit their biological activity.

Excrete Poorly Soluble Organic Ions

Many organic ions are not very soluble (they are hydrophobic) and circulate within the plasma bound to carrier proteins. Since large proteins aren't filtered, only the fraction that isn't carrier-bound can enter the glomerular filtrate. Tubular secretion further removes the small, unbound fraction of the organic ions, which causes even more "unloading" of the organic ion from its carrier molecule. In this manner, organic ions highly bound to carrier proteins can be excreted.

Removal of Foreign Compounds

In addition to endogenous organic ions, many foreign organic ions such as food additives, drugs, pesticides, environmental pollutants, and more, need to be removed from the body. The kidneys routinely remove these compounds, but there are no regulatory mechanisms in place to increase their removal if necessary.

QUESTION: TRANSPORT ACROSS THE PROXIMAL AND DISTAL NEPHRON

This content was retrieved from Section 05, Slide 9 of 9 of the online learning module.

This completes our overview of the re-absorptive and secretory processes that occur across the proximal and distal portions of the nephron. Overall, the proximal tubule is responsible for most of the reabsorption, as it transfers much of the filtered water and needed solutes back into the blood in an unregulated fashion. The distal and collecting tubules determine the final amounts of H₂O, Na⁺, K⁺, and H⁺ that will be eliminated by the body through processes that are subject to control.

Using what you have learned regarding the reabsorption of solutes in the proximal tubule, distal tubule, and collecting duct, indicate if the following statements are true or false.

Statements:

- In the proximal tubule, roughly 67% of Na⁺ is actively reabsorbed.
- No filtered glucose is reabsorbed within the proximal tubule.
- All H₂O is reabsorbed within the distal tubule and collecting duct.
- There are variable amounts of PO₄³⁻ reabsorbed within the proximal tubule.

Feedback:

- In the proximal tubule, roughly 67% of Na⁺ is actively reabsorbed. -True
- No filtered glucose is reabsorbed within the proximal tubule. - False
- All H₂O is reabsorbed within the distal tubule and collecting duct. - False
- There are variable amounts of PO₄³⁻ reabsorbed within the proximal tubule. - True

SECTION 06: PLASMA CLEARANCE AND URINE EXCRETION**SECTION 06: PLASMA CLEARANCE AND URINE EXCRETION**

This content was retrieved from Section 06, Slide 1 of 23 of the online learning module.

By the end of Section 06, you should be able to:

- Describe what is meant by plasma clearance.
- Describe what is meant by the vertical osmotic gradient and why it is important.
- Describe the role of the loop of Henle and why its structure is important for its function.
- Describe countercurrent exchange.
- Describe the micturition reflex.

Assigned Readings:

Human Physiology: From Cells to Systems, 3rd Canadian Edition

By Sherwood and Ward

Chapter 13: Pages 585-601

PLASMA CLEARANCE

This content was retrieved from Section 06, Slide 2 of 23 of the online learning module.

Recall that a healthy person filters 125 m l/min of plasma. Now factor in that 124 m l/min are reabsorbed, which leaves the final amount of urine produced to be 1 m l/min or 1.5 L/day. During this reduction in volume there is a concentration of waste products and other substances that are to be excreted in the urine.

When we compare the plasma in the renal arteries to the renal veins, many substances have been eliminated in the urine.

These substances have been “cleaned” or cleared from the plasma. This is the concept of **plasma clearance** which can be defined for any substance as the volume of plasma cleared of that substance by the kidneys per minute. Note that the unit of plasma clearance is volume of plasma, not the amount of the substance. Plasma clearance expresses the effectiveness of the kidneys to remove a substance from the internal fluids.

It is calculated by this equation:

Clearance rate (m l/min) = urine concentration (quantity/m l) x urine flow rate (m l/min) / plasma concentration (quantity/m l)

TYPES OF PLASMA CLEARANCE

This content was retrieved from Section 06, Slide 3 of 23 of the online learning module.

The plasma clearance rate varies for different substances, depending on how the kidneys handle each substance.

These variations in plasma clearance can be classified into three types.

Learn about the various types of plasma clearance experienced by a substance.

Substances that are filtered, not reabsorbed - Refer to page 45

Substances that are filtered and reabsorbed - Refer to pages 45-46

Substances that are filtered and secreted, not reabsorbed - Refer to page 46

FILTERED, NOT REABSORBED

Subpage of Section 06, Slide 3 of 23 – Substances that are filtered, not reabsorbed - 1/1

Often used as an example to calculate plasma clearance is the substance inulin, which is an exogenous carbohydrate found in onions and garlic. It is freely filtered, but neither reabsorbed or secreted, so its plasma clearance is used to estimate glomerular filtration rate. Since all glomerular filtrate is cleared of inulin, the volume of plasma cleared per minute of inulin equals the volume of plasma filtered per minute.

Review the calculation:

Clearance rate for inulin

$$= (30 \text{ mg/ml urine} \times 1.25 \text{ ml urine/min}) / 0.3 \text{ mg/ml plasma}$$

$$= 125 \text{ ml/min}$$

It is difficult to use inulin because it must be continually injected to maintain a steady plasma concentration. Therefore, the endogenous substance creatine is generally used clinically to determine glomerular filtration rate. As an end product of muscle metabolism, its plasma concentration is relatively steady and not reabsorbed with only minor secretion.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

FILTERED AND REABSORBED

Subpage of Section 06, Slide 3 of 23 – Substances that are filtered and reabsorbed - 1/1

For substances that are reabsorbed, the plasma clearance has to be less than the glomerular filtration rate. Let's use two substances we looked at for tubular reabsorption as examples, glucose and urea.

For glucose, it is normally totally reabsorbed so none of the plasma is cleared of glucose. Its plasma clearance is 0.

In contrast, for urea, which is partially reabsorbed (recall 50%), only about half of the filtered plasma is cleared of urea. Its plasma clearance is 62.5 ml/min.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

FILTERED, SECRETED, NOT REABSORBED

Subpage of Section 06, Slide 3 of 23 – Substances that are filtered and secreted, not reabsorbed - 1/1

For this type of substance, the plasma clearance will be greater than the glomerular filtration rate.

We have recently talked about hydrogen ion tubular secretion. If we take the amount of secreted H⁺ to be the amount of H⁺ in 25 m l of plasma, and a glomerular filtration rate of 125 m l/min, we can calculate the plasma clearance of H⁺ to be 150 m l/min.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: PLASMA CLEARANCE

This content was retrieved from Section 06, Slide 4-5 of 23 of the online learning module.

Using what you have learned about the molecules involved in determining plasma clearance, select whether the molecules below are secreted and/or reabsorbed.

- Hydrogen Ions
- Glucose
- Urea
- Inulin

Feedback:

- Hydrogen Ions - Secreted
- Glucose - Reabsorbed
- Urea - Reabsorbed
- Inulin - Neither

THE KIDNEYS AND URINE CONCENTRATION

This content was retrieved from Section 06, Slide 6 of 23 of the online learning module.

So far in this module we have talked about how substances are filtered, reabsorbed, and secreted for the purpose of either retaining them within the body, or eliminating them through the urine. We will now learn about how the kidneys deal with plasma water in order to produce urine of different concentrations. The fundamental principle of concentrating urine is osmosis. The ECF osmolarity depends on the relative amount of water compared to solute. The same principle applies to tubular fluid

Given that water moves by osmosis, you would expect a concentrated urine to osmotically draw water from the surrounding tissues. How then do the kidneys produce a concentrated urine? The ability to concentrate urine occurs because there is a **vertical osmotic gradient** in the interstitial fluid of the medulla.

Review a note on the vertical osmotic gradient.

The normal osmolarity of ECF fluids in the body are 300 mOsm/L. In the cortex, the interstitial fluid osmolarity is 300 mOsm/L but in the medulla, as you move from the cortex to the renal pelvis, there is a gradual gradient as the interstitial fluid osmolarity goes from 300 mOsm/L to 1200 mOsm/L. By mechanisms that we will soon explore, this gradient allows the kidneys to produce urine with an osmolarity range of 100 mOsm/L to 1200 mOsm/L, depending on the hydration state of the body.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: HOW THE KIDNEYS USE THE VERTICAL OSMOTIC GRADIENT

This content was retrieved from Section 06, Slide 7-8 of 23 of the online learning module.

Several unique anatomical arrangements allow the kidneys to use this vertical osmotic gradient to alter the concentration of the urine. In Section 02 of this module, we explored the two different types of nephrons and their structural differences.

What are the structural differences of these two different types of nephrons, specifically with reference to the Loop of Henle?

Cortical

Juxtamedullary

Feedback:

Cortical: The loop of Henle only dips slightly into the medulla.

Juxtamedullary: The loop of Henle dips all the way down to the renal pelvis. The vasa recta of these nephrons also goes all the way to the renal pelvis. Flow in the loop of Henle and the vasa recta goes in opposite directions in what is called countercurrent flow.

*In both types of nephrons, the descending collecting ducts that go all the way to the renal pelvis. These anatomical arrangements, coupled with the permeability and transport properties of the different sections of the tubule, are what allow the kidneys to make urine of different concentrations. The loops of Henle establish the vertical osmotic gradient, the vasa recta preserve the gradient, and the collecting ducts use the gradient, along with vasopressin, to produce urine of varying concentrations. Collectively, this is known as the **medullary countercurrent system**. We will now see how it all works in greater detail.*

THE MEDULLARY VERTICAL OSMOTIC GRADIENT

This content was retrieved from Section 06, Slide 9 of 23 of the online learning module.

We will follow the flow of filtrate through a juxtamedullary (long loop) nephron to see how this structure establishes the vertical osmotic gradient.

Learn about the steps involved in establishing this gradient.

1. As soon as the fluid leaves Bowman's capsule and enters the proximal tubule, there is a strong drive for osmotic reabsorption of water secondary to the active reabsorption of Na^+ . Remember, water follows Na^+ .
2. By the end of the proximal tubule, due to Na^+ reabsorption, 65% of the filtrate volume has been reabsorbed. What is important to note, however, is that the osmolarity of the tubular fluid at this point is 300 mOsm/L, or isotonic, to other bodily fluids.
3. In the loop of Henle, an additional 15% of the filtered water will be reabsorbed during the establishment and maintenance of the vertical osmotic gradient. The descending and ascending limbs of the loop of Henle are distinct in their function. Ascending limbs are impermeable to water, but reabsorb Na^+ . In this case, water does not follow Na^+ . The descending limbs, however, are highly permeable to water, but do not reabsorb Na^+ .

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

MECHANISM OF COUNTERCURRENT MULTIPLICATION

This content was retrieved from Section 06, Slide 10 of 23 of the online learning module.

Because the descending and ascending limbs are in close proximity, important interactions occur between them in order to establish the vertical osmotic gradient. This process occurs because filtrate is constantly flowing, but we will now look at it as if we start with a medulla without an osmotic gradient to understand how such a gradient is established.

We will hypothetically show six steps of fluid movement through the loop of Henle.

Review the initial step of fluid movement and the six steps thereafter.

1. Fluid from the proximal tubule entering the descending loop of Henle is 300 mOsm/L and the interstitial space is also 300 mOsm/L. The descending limb allows both Na^+ and water to pass, but since it is isotonic to the interstitial space, there is no net movement."
2. Due to the close proximity of the ascending limb, which actively reabsorbs Na^+ but not water, Na^+ moves into the interstitial space. Na^+ can move until the interstitial fluid is 200 mOsm/L more concentrated than the ascending limb entering the distal tubule. So from the perspective of the ascending limb, the tubular fluid is 200 mOsm/L and the interstitial fluid is 400 mOsm/L. Because both Na^+ and water can move across the descending limb wall, the osmolarity of the initial part of the descending limb equilibrates (remains isotonic to) the interstitial fluid so the tubular fluid in the descending limb is also now 400 mOsm/L.
3. As new fluid moves into the descending loop of Henle, the fluid all shifts forward so we now have 300 mOsm/L entering the descending limb, pushing the 400 mOsm/L fluid deeper into the medulla. As the 400 mOsm/L fluid moves around to the ascending limb, Na^+ is reabsorbed until an osmotic difference OF 210 mOsm/L is again established. Note, however, that we no longer have a 200 mOsm/l difference between descending and ascending limb fluids.
4. While the ascending limb is still transporting Na^+ out, water continues to passively leave the descending limb until the 200 mOsm/L difference between the descending and ascending limbs is established at each horizontal level. Notice how the concentration of the tubular fluid in the descending limb is gradually increasing to remain isotonic to the interstitial fluid, yet the fluid in the ascending limb is gradually decreasing to maintain the 200 mOsm/L difference.
5. As fresh 300 mOsm/L fluid enters the descending loop, all the fluid moves forward disrupting the concentration gradient at all vertical levels until it again equilibrates.
6. Again, fresh filtrate enters, the osmolarity of the interstitial fluid increases, and the osmolarity of the ascending loop fluid decreases to maintain the 200 mOsm/L difference.

7. Eventually, equilibrium is achieved such that even with 300 mOsm/L filtrate entering the descending limb, there is a vertical osmotic gradient that results in the tubular fluid being 1200 mOsm/L as it enters the ascending limb, and the tubular fluid is 100 mOsm/L as it enters the distal tubule. The maximum osmolarity is four times greater than the normal osmolarity of body fluids, while the osmolarity leaving the ascending limbs is one-third of normal osmolarity.

Please note that once the incremental medullary gradient is established, it remains constant due to the continuous flow of fluid and solute transport.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: MECHANISM OF COUNTERCURRENT MULTIPLICATION

This content was retrieved from Section 06, Slide 11 of 23 of the online learning module.

Order the steps of countercurrent multiplication in the loop of Henle.

Step of Countercurrent Multiplication:

- 200 m O s m /L gradient is first established between the interstitial fluid and the ascending limb
- Fluid flows forward several frames again
- 200 m O s m /L gradient is established once again at each horizontal level
- Ascending and descending limbs reestablish the 200 m O s m /L gradient
- Fluid flows forward several frames
- Vertical osmotic gradient is established and maintained in an ongoing fashion

Feedback:

1. 200 m O s m /L gradient is first established between the interstitial fluid and the ascending limb
2. Fluid flows forward several frames
3. Ascending and descending limbs reestablish the 200 m O s m /L gradient
4. Fluid flows forward several frames again
5. 200 m O s m /L gradient is established once again at each horizontal level
6. Vertical osmotic gradient is established and maintained in an ongoing fashion

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

WHAT IS THE PURPOSE OF COUNTERCURRENT MULTIPLICATION?

This content was retrieved from Section 06, Slide 12 of 23 of the online learning module.

If you consider only what happens to the tubular fluid as it flows through the loop of Henle, the whole process seems to be pointless.

The isotonic fluid that enters the loop becomes progressively more concentrated as it flows down the descending limb, only to become progressively more dilute as it flows up the ascending limb.

This mechanism offers two benefits. First, it establishes a vertical osmotic gradient in the medullary interstitial fluid. This gradient allows the collecting ducts to both form more concentrated and more dilute urine than normal bodily fluids. And lastly, it allows for the overall volume of urine to be significantly reduced, which also allows the body to conserve both salt and water. We will explore this on the next few slides.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

VASOPRESSIN-CONTROLLED WATER REABSORPTION

This content was retrieved from Section 06, Slide 13 of 23 of the online learning module.

In this module so far, we have only mentioned vasopressin, but we will now discuss it in detail.

Learn how vasopressin is able to control water reabsorption.

1. Recall from Module 07 that vasopressin, or antidiuretic hormone, is a hormone released from the posterior pituitary gland. It is released in response to a water deficit, when the ECF is hypertonic. Its release is inhibited when the ECF is hypotonic.
2. Once released into the circulation, it travels to the kidneys where it acts on distal tubular cells to increase the number of aquaporin molecules in the luminal membrane. This increases the amount of water reabsorbed into the epithelial cells.
3. Once inside the epithelial cells, water passively moves into the interstitial fluid and plasma. Vasopressin has no actions on the proximal tubule or the loop of Henle where 80% of water is reabsorbed. Therefore, it can only increase water reabsorption in the distal and collecting tubules.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

REGULATION OF WATER REABSORPTION

This content was retrieved from Section 06, Slide 14 of 23 of the online learning module.

Tubular fluid entering the distal tubule is around 100 mOsm/L, yet the interstitial fluid of the renal cortex is 300 mOsm/L and gets even higher, approaching 1200 mOsm/L around the collecting tubules, as they plunge towards the renal pelvis. These gradients mean that water wants to leave the tubular fluid due to osmosis, but it can only do so in the presence of vasopressin.

Learn how vasopressin is able to regulate water reabsorption under two conditions.

Deficit of Water

When someone is very dehydrated, the release of vasopressin will increase the number of aquaporin channels in the distal and collecting tubules. Under the maximum influence of vasopressin, the osmolarity of the tubular fluid at the end of the collecting ducts can be up to 1200 mOsm/L, isotonic to

the interstitial fluid. This is the maximum concentration of urine that can be achieved by the body. Urine production can be reduced to as little as 0.3 m l/min.

Excess of Water

In this case, the body fluid osmolarity is below 300 mOsm/L. The tubular fluid entering the distal tubule is still 100 mOsm/L.

When the body fluids are so hypotonic that vasopressin secretion is completely suppressed, this prevents the insertion of aquaporins in the luminal membrane of the distal and collecting tubules so no water is reabsorbed. In this manner, urine with an osmolarity of 100 mOsm/L can be produced with a volume of up to 25 ml/min.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

QUESTION: HOW DOES THE KIDNEY PRODUCE SUCH A LARGE RANGE OF URINE CONCENTRATION?

This content was retrieved from Section 06, Slide 15-16 of 23 of the online learning module.

As you have learned, the vertical osmotic gradient allows for the production of both more concentrated and more dilute urine than normal bodily fluids. How is this possible?

Feedback:

Recall that the ascending loop of Henle always makes the tubular fluid very hypotonic by reabsorbing Na⁺, but not water. In this way, it ensures that the tubular fluid is always hypotonic to the interstitial fluid, no matter how much water excess there is. The fact that the tubular fluid is hypotonic as it enters the distal parts of the tubule allows the kidneys to excrete a urine more dilute than normal bodily fluids, as vasopressin release is suppressed, prevent water reabsorption. In the case that water needs to be conserved, vasopressin release can cause the tubular fluid to become more concentrated before excretion. Therefore, the loop of Henle, by simultaneously establishing the medullary osmotic gradient and diluting the tubular fluid before it enters the distal segments, plays a key role in allowing the kidney to excrete urine that ranges in concentration from 100 to 1200 mOsm/L.

COUNTERCURRENT EXCHANGE WITHIN THE VASA RECTA

This content was retrieved from Section 06, Slide 17 of 23 of the online learning module.

The vasa recta, the blood supply to the renal medulla, supports the countercurrent multiplier mechanism, due to a few important characteristics. First, the vasa recta is closely associated with the descending and ascending loops of Henle, in part due to the hairpin shape that allows it to dive down into the medulla. The vasa recta is also highly permeable to NaCl and H₂O, and the blood flow through the vasa recta is opposite, or countercurrent, to fluid flow through the loop of Henle.

The vasa recta travel through the medulla where the interstitial fluid osmolarity can be 1200 mOsm/ml. What effect does this have of the composition of the blood in the vasa recta?

Review the answer to this question. - Refer to page 52

This process of passive solute and H₂O exchange between the two limbs of the vasa recta and the interstitial fluid is known as **countercurrent exchange**. This is different from the countercurrent multiplication of the loop of Henle in that flow does not establish the current gradient. Blood enters the medulla for nutrient exchange, yet the hypertonic gradient of the medulla is preserved.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

COUNTERCURRENT EXCHANGE

Subpage of Section 06, Slide 17 of 23 – Review the answer to this question - 1/1

Review the changes in the osmolarity of the blood in the vasa recta.

1. As efferent arteriolar blood leaves the renal cortex, its osmolarity is 300 mOsm/L, isotonic to the interstitial fluid.
2. As the descending loop moves towards the renal pelvis, the plasma remains isotonic to the surrounding interstitial fluid by reabsorbing Na⁺ and water leaving.
3. At the bottom of the loop, the plasma osmolarity is 1200 mOsm/L.
4. As the blood flows up the ascending limb, the opposite occurs with water being reabsorbed and Na⁺ leaving, to keep the plasma isotonic with the different levels of the medulla.
5. As the vasa recta re-enters the cortex its osmolarity is back to 300 mOsm/L, again isotonic to the interstitial fluid.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

WATER REABSORPTION

This content was retrieved from Section 06, Slide 18 of 23 of the online learning module.

Although we've been over water reabsorption, the last topic we need to discuss is the importance of distinguishing between water reabsorption that mandatorily follows solute reabsorption, and water reabsorption that is independent of solute reabsorption.

In the tubular segments permeable to water, solute reabsorption always leads to water reabsorption due to osmosis. The opposite is also true, in that solute excretion is always accompanied by water excretion, again due to osmosis. When there is excess, un-reabsorbed solute in the tubular fluid, it exerts an osmotic influence to retain excessive water in the tubule. This is the phenomenon of osmotic diuresis, which increases urinary excretion. There are two types of diuresis, osmotic diuresis and water diuresis.

Learn about the two types of diuresis.

Osmotic Diuresis

Osmotic diuresis is the increased excretion of both water and excess un-reabsorbed solute. This is seen in diabetics with glucose levels high enough that not all of the filtered glucose is reabsorbed.

The excess glucose in the tubules attracts water and increases urine production. This is why a symptom of diabetes is excess urine production.

Water Diuresis

This is the increased excretion of water when there is little or no change in the excretion of solutes. This is what occurs following alcohol consumption as vasopressin secretion is suppressed. This causes the kidneys to excrete a dilute urine, generally in volume greater than the alcohol consumed, which explains how you can become dehydrated by drinking alcohol.

URINE STORAGE

This content was retrieved from Section 06, Slide 19 of 23 of the online learning module.

Now that we have finished our discussion of kidney function, the rest of this module will focus on urine transport and storage. Once formed in the kidneys, urine is transmitted through the ureters by peristaltic contractions to the bladder. Urine does not normally flow backwards towards the kidneys, but it is possible if enough pressure is generated.

Learn about the roles of the bladder, and the internal and external urethral sphincters.

The Bladder

The bladder is composed of smooth muscle with a specialized epithelial lining, and is capable of expanding to increase storage capacity. It is highly innervated by the parasympathetic nervous system, the stimulation of which causes bladder contraction. The exit through the urethra is guarded by the internal urethral sphincter and the external urethral sphincter.

The Internal Urethral Sphincter

The internal urethral sphincter is under involuntary control. Although it is really part of the bladder wall and not a true sphincter, when the bladder is relaxed, the internal urethral sphincter closes the outlet to the urethra.

The External Urethral Sphincter

The external urethral sphincter encircles the urethra and is supported by the pelvic diaphragm. This sphincter is kept closed by a constant, tonic firing of motor neurons. Because it is comprised of skeletal muscle, it is under voluntary control in that it can be deliberately tightened to prevent urination, even when the bladder contracts.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

MICTURITION (URINATION) REFLEX

This content was retrieved from Section 06, Slide 20 of 23 of the online learning module.

Micturition, or urination, is the process of the bladder emptying, and is governed by two mechanisms: the micturition reflex and voluntary control.

Learn about these mechanisms.

Micturition Reflex

The micturition reflex can be overridden by voluntary control. By learning the perception of bladder filling prior to the activation of the reflex, voluntary excitatory signals from the cerebral cortex can override the micturition reflex. This can only continue for so long, however, as urine production is constant and eventually the pressure-activation of the reflex is stronger than voluntary control and the bladder uncontrollably empties.

Voluntary Control

The adult bladder normally holds between 250 and 400 ml before the internal pressure on the bladder wall initiates the micturition reflex. The stretch activates afferent fibres to the spinal cord where interneurons activate the parasympathetic system to stimulate bladder contraction and relaxation of the external sphincter.

There is no mechanism to open the internal sphincter, it does so as the bladder changes shape during contraction. With both sphincters open, urine is expelled. This micturition reflex is evident in infants; as soon as their bladders fill enough to activate it, urine is released.

Reference:

Sherwood, L. (2015). *Human Physiology: From Cells to Systems*. Nelson Education

SUMMARY

This content was retrieved from Section 06, Slide 21 of 23 of the online learning module.

In Module 04, we learned about how the kidneys regulate homeostasis within the body. These organs are responsible for the regulation of electrolyte composition, volume, osmolarity, and pH of the internal environment.

Throughout this module, we started by gaining an understanding of the responsibility of the kidneys by first examining their anatomy and physiology, to then continue on to learn about their role in the balance and regulation of substances such as water, sodium, plasma, electrolytes, glucose, and phosphate. We explored the major structures of a juxtaglomerular nephron and discuss the importance of each section with respect to reabsorption and secretion.

Next, we investigated blood flow through the kidneys and its physiological importance in the generation of urine. We expanded our knowledge of osmotic gradients, and described how the kidney can make urine either more dilute or more concentrated than other bodily fluids.

Finally, using dehydration as an example, we learned about the physiological responses and processes that occur in order to reduce water loss through urine production.

In Module 05, will learn about the importance of acid-base balance and how it is maintained within the body.

MODULE 04: IMPORTANT FORMULAS

This content was retrieved from Section 06, Slide 22 of 23 of the online learning module.

View each formula:

Plasma Clearance Rate:

Clearance rate (m l/min) = urine concentration (quantity/m l) x urine flow rate (m l/min) / plasma concentration (quantity/m l)

Glomerular Filtration Rate:

Filtration Coefficient (K_f) x Filtration Pressure = Glomerular Filtration Rate

Net Filtration Pressure:

Filtration Coefficient (K_f) x Filtration Pressure = Glomerular Filtration Rate

LEARNING OUTCOMES

This content was retrieved from Section 06, Slide 23 of 23 of the online learning module.

Now that you have completed Module 04, you should be able to:

1. Describe the major structures of a juxtaglomerular nephron and discuss the importance of each section with respect to reabsorption and secretion.
2. Describe blood flow through the kidneys and its physiological importance in the generation of urine.
3. Using your knowledge of osmotic gradients, describe how the kidney can make urine either more dilute or more concentrated than bodily fluids.
4. Using dehydration as an example, describe the physiological responses and processes that occur in order to reduce water loss through urine production.

CONCLUSION

END OF MODULE 4: COMPLETE!

This content was retrieved from Conclusion, Slide 1 of 1 of the online learning module.

Section 01: Introduction to Renal Physiology and Water Balance

Section 02: Overview of the Kidneys

Section 03: Glomerular Filtration

Section 04: Tubular Reabsorption

Section 05: Tubular Secretion

Section 06: Plasma Clearance and Urine Excretion