Exam KEY

NROSCI / BIOSC 1070 -- MSNBIO2070
Exam # 2
October 26, 2018

Total POINTS: 100 20% of grade in class

1) Prazosin is a selective antagonist for α_1 receptors, while Phenoxbenzamine is an antagonist for both α_1 and α_2 receptors. Neither drug crosses the blood brain barrier and acts in the central nervous system.

a) Which of the following effects on the heart are produced by the drugs (circle the correct answer; ***2 points***)?

Negative Chronotropic and Negative Inotropic

Positive Chronotropic and Positive Inotropic

Negative Chronotropic and Positive Inotropic

Positive Chronotropic and Negative Inotropic

No Inotropic or Chronotropic Effects

b) Which of the drugs, if either, produces the largest effects on the heart? Provide a justification for your answer. ***(6 points)***.

Both drugs reduce blood pressure, activating the baroreceptor reflex and increasing sympathetic actions on the heart, causing positive chronotropic and inotropic effects. Phenoxbenzamine blocks α_2 receptors on sympathetic nerve terminals, which enhances the sympathetic actions on the heart.

2) During an experiment on an anesthetized animal, which is artificially ventilated to maintain stable blood oxygenation, 20% of the blood volume is removed. Physiological parameters are measured at 5 minutes and 2 hours following the blood removal. Answer the following questions about the physiological changes that are determined.

a) Is heart rate higher, lower, or the same at 5 minutes after the blood removal than before the blood removal? Provide a brief justification for your answer. ***(5 points)***.

Higher, due to the baroreceptor reflex activation by reduced blood pressure.

b) Blood volume is higher at 2 hours following the blood removal than at 5 minutes following the blood removal, but lower than before the blood removal. Explain the main factor causing blood volume to return towards normal at 2 hours following the blood removal, even though the animal is provided no fluid. ***(5 points)***.

Engagement of the baroreceptor reflex causes pre-capillary smooth muscle (in arterioles) to constrict. As a result, capillary hydrostatic pressure drops, such that absorption is favored over filtration. Consequently, fluid is pulled from the interstitial space into the vascular compartment.

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Question 2, Continued

c) Is hematocrit different at 2 hours following the blood removal different than at 5 minutes following the blood removal? Provide a brief justification for your answer. ***(3 points)***.

Yes, it is lower. As fluid is pulled into the intravascular space from the interstitial space, the % of blood occupied by RBCs drops.

3) A blood sample is taken from an astronaut living on the International Space Station, and hormone levels are compared to those for the individual prior to leaving Earth Discuss the changes in the levels of the following physiological parameters after a prlonged exposure to microgravity. ***(1 point each; 4 points total).***

Atrial Natriuretic Peptide Levels:	Lower	Higher	The Same
Angiotensin II Levels:	Lower	Higher	The Same
Aldosterone Levels:	Lower	Higher	The Same
Vasopressin Levels:	Lower	Higher	The Same

4) Sheer stress along an arteriole wall and pressure on the arteriole wall elicit opposite changes in resistance of the vessel. Briefly describe the change in resistance evoked by each force, and the physiological mechanism that mediates the response ***(6 points total).***

Sheer stress activates nitric oxide synthase by opening Ca^{2+} channels or activating mechanoreceptors on the endothelial cell surface. NO that is synthesized in the endothelial cell diffuses into the adjacent smooth muscle cells, causing relaxation and decreased resistance.

Pressure opens stretch-sensitive Na^{+} channels in the smooth muscle cells. Na+ enters and depolarizes the smooth muscle cells, causing voltage-gated Ca^{2+} channels to open. The entry of Ca^{2+} causes constriction and increased resistance.

5) NATRECOR® is a natriuretic peptide indicated for the treatment of patients with acutely decompensated heart failure. The most severe side effect of NATRECOR® is a sudden drop in blood pressure. Briefly explain the mechanism through which NATRECOR® can produce hypotension. ***(4 points total).***

Natriureric peptifdes cause dilation of both arterioles and veins, decreasing TPR and increasing venous compliance, thereby lowering blood pressure (2.5 points for each). It is also OK to indicate that blood volume is lowered.

6) Millions of Americans are taking drugs to lower their blood LDL-cholesterol levels. Answer the following questions regarding these drugs.

a) Why is important to maintain low blood LDL-cholesterol levels? What are the negative physiological consequences of high blood LDL-cholesterol? ***(5 points).***

High-LDL cholesterol can damage the walls of arteries, leading to atherosclerosis and arterial narrowing. The convoluted lining of the blood vessels can lead to formation of blood clots, which can dislodge and block the artery downstream.

b) For the past two decades, drugs called statins such as Lipitor, Mevacor, and Crestor have been prescribed to lower LDL-cholesterol levels. How do these drugs work to produce this effect? ***(5 points).***

The drugs are HMG-COA reductase inhibitors. They reduce the endogenous synthesis of cholesterol

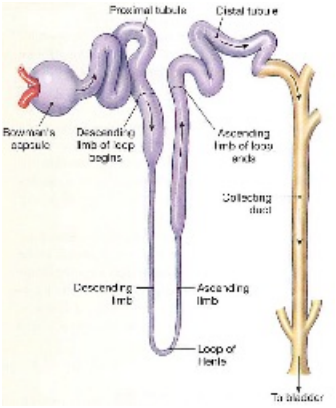
c) The latest treatment for patients with high blood LDL-cholesterol is proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. Briefly describe how these drugs act to reduce blood LDL-cholesterol levels in patients that are unresponsive to conventional therapies. ***(5 points).***

PCSK9 inhibitors block the signaling protein that tags the LDL-receptor for destruction. As a result, these drugs cause the number of LDL receptors to be increased.

7) Sketch a schematic figure of a cortical nephron and label the major segments. ***(2 points)*.**

a) In each segment note the osmotic concentration (assuming an ADH level of ~3 pg/ml). ***(5 points)***.

b) Assuming a creatinine concentration of 1 mg/ml in plasma, describe the albumin/creatinine ratio at each segment of the nephron. Assue that albumin concentrations in serum is approximately 35 - 50 g/L. ***(5 points)***.

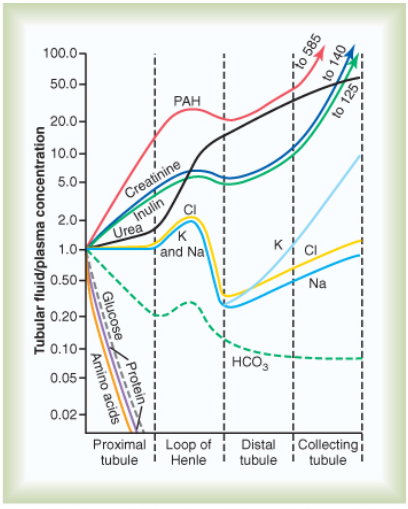


Must label the proximal tubule, loop of Henle, distal tubule, and collecting duct (0.5 points each). It is OK to divide the loop of Henle into the descending and ascending limb.

a) With this level of ADH, the final urine osmolarity is about 600 mOsm. These are the critical numbers to include (1 pt each):

Proximal tubule: 300 mOsm (1 pt)
Loop of Henle: 600-1200 mOsm (anything in that range is OK; 1 pt)
Distal convoluted tubule: 100 mOsm (1 pt)
Distal collecting duct: 600 mOsm (2 pts)

*b) Albumin levels in the filtrate are ordinarily very low, but all the filtered albumin is reabsorbed in the proximal tubule. Creatinine is not secreted nor reabsorbed. Thus, albumin/creatinine ratio is highest in the proximal tubule, but is 0 elsewhere in the tubule (as there is no albumin). If you said that albumin is not filtered substantially (so the albumin/creatinine ratio is 0 through the nephron, you also get full credit). **5 points.***



8) A new superhero was created who has unusually long loops of Henle. What special powers does this superhero have? Explain your answer. ***(5 points).***

The long loops of Henle would allow even a higher interstitial osmolarity to be generated. As a result, urine could be concentrated more than normal.

9) The hormone aldosterone plays an important role in renal system regulation. Answer the following questions about this hormone.

a. What are the <u>two</u> main factors that stimulate the release of aldosterone? ***(2 points each; 4 points total).***

1) Levels of angiotensin II
2) Levels of plasm K+

b. Describe the actions of aldosterone in the kidney (indicate which segment and which cells it acts on, and the responses when aldosterone binds to its receptor). **(*5 points).***

Aldosterone binds to intracellular receptors, mainly in the principal cells of the distal nephron (1 pt; OK to just indicate distal nephron or collecting duct).

Through genomic actions, the hormone:
increases the activity of Na+/K+ ATPase (or increases the amount of ATPase in the basolateral membrane) -- 1 pt
causes the production of more apical membrane sodium and ROMK channels – 1 pt

As a result, there is more reabsorption of sodium and water, and more secretion of K+ into the tubular lumen (2 pts).

10) What is meant by the term "renal filtration fraction," and how would you measure its value by determining the clearance of particular substances? ***(9 points).***

Filtration fraction is the ratio of the glomerular filtration rate (GFR) to the renal plasma flow (RPF): FF = GFR/RPF .

Often PAH (para-aminohippurate) is used to estimate renal blood flow. PAH is freely filtered, is not reabsorbed, and is secreted within the nephron. Thus, PAH is cleared from the blood in one pass through the kidney. By determining plasma and urine levels of PAH and urine production rate, renal blood flow can be ascertained:

RPF = Urine(PAH) Urine Production Rate / Plasma(PAH)*

GFR is determined using a substance that is filtered but not secreted or reabsorbed, such as inulin or creatinine:

GFR = Excretion of inulin / Plasma inulin

Key points:

3 points: FF = GFR / RPF.
3 points: noting that RPF is determined via the use of a substance (like PAH) that is both freely filtered and secreted, so it is eliminated in one pass through the kidney.
3 points: noting that GFR is determined using a substance (like inulin) that is filtered but neither secreted or reabsorbed.

11) Describe the actions of three drugs that could serve as diuretics. For each drug, indicate the negative actions (side effects) that could be result from its use. ***(5 points for each drug; 15 points total).***

Any three of the following. For each, 3 pts for describing the action and 2 pts for the side effects.

Osmotic diuretics
Freely fliteres substances that are neither reabsorbed or secreted. They increase the osmolarity of the tubular fluid, and thus lead to diuresis.

Side effects: 1) Lead to initial plasma expansion (due to movement of fluid from the interstital space) and thus an increase in blood pressure and 2) Leads to Hypernatremia (high plasma sodium)

Loop diuretics
Inhibit the sodium-potassium-chloride cotransporter in the thick ascending limb.

Side effects: 1) Hyponatremia and 2) Hypokalemia (OK to just say hypokalemia)

Thiazide Diuretics
Inhibit the sodium-chloride transporter in the distal tubule.

Side effects: 1) Hyponatremia and 2) Hypokalemia (OK to just say hypokalemia)

Potassium-Sparing Diuretics
Act on cells in the collecting duct to either block the apical membrane sodium channels or antagonize the aldosterone receptor.

The most serious side effect of both is hyperkalemia.

Note: this could count as two separate drugs (sodium channel blockes + aldosterone receptor antagonist).

Carbonic Anhydrase Inhibitors
By inhibiting carbonic anhydrase, transport of bicarbonate is attenuated. Thus, bicarbonate rises in the urine and H+ rises in the plasma.

The main side effect is urine alkalinization (which could cause kidney stones) and metabolic acidosis.

ACE inhibitors or Angiotensin-II receptor blockers
These drugs are not classic diuretics but can lead to diuresis. These drugs inhibit aldosterone production and inhibit sodium reabsorption throughout the kidney.

Side effects: hyperkalemia and low blood pressure.