READ THIS PAGE BEFORE YOU BEGIN THE EXAM.

1. Write your name on every page. (5 points off for EACH unnamed page.)
2. Do NOT write on the BACK of any page unless you get a TA’s permission FIRST.
3. About writing answers:
   • All questions can be answered briefly.
   • For full credit, discuss mechanisms.
   • In problems asking for an answer and a reason, more credit is given for a correct reason.
4. Use a pen or pencil to write your answers, but do NOT use RED INK and DO NOT USE
   WHITE-OUT of any kind. However, if you use pencil, you cannot request a regrade.

POTENTIALLY USEFUL EQUATIONS:

\[ F = A \eta \frac{\Delta V}{\Delta X} \]
\[ R = \frac{8 \eta l}{\pi r^4} \]
\[ Q = \frac{(P_2 - P_1) \pi r^4}{8 \eta l} \]
\[ J = -PS(C_{out} - C_{in}) \]
\[ J = k[(P_{cap} + \pi_{int}) - (P_{int} + \pi_{cap})] \]
\[ R = \pi \alpha RT(C_0 - C_i) \]
\[ v = \frac{Q}{A} \]
\[ E_x = \frac{RT \ln [X^+]_{out}}{ZF} \]
\[ \frac{1}{R_{Total}} = \sum \frac{1}{R_i} \]

SCORE:

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Page 3 _________
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Page 7 _________
TOTAL _________

WAIVER: By signing this waiver I give permission that this exam can be left for me to pick up in the hall across from the elevator on the third floor of Pacific Hall. I realize that this procedure may expose my grade to public scrutiny and my exam to theft. **If I do not sign this waiver, I understand I will be able to get my graded exam back only as described in on the course Web site.**

__________________________  __________________
Signature                     PID
1. (11 points total) Use GnRH and ADH as examples to distinguish a releasing factor from a hormone. In particular:

A. (4 points) Discuss two major ways that a hormone differs from a releasing factor.

There are many possible answers; among them are:
1. The targets of GnRH are other endocrine cells; the targets of ADH are non-endocrine (kidney and vascular smooth muscle) cells.
2. The effect of GnRH is the release of another releasing factor (FSH, LH); the effects of ADH is to modify the function of the target cells.

Less major or less general differences:
1. Releasing factors are always peptides; many hormones are steroids.
2. GnRH acts through the anterior pituitary; ADH acts through the posterior pituitary.

B. (4 points) Discuss two major ways that a hormone is similar to a releasing factor.

Again, lots of possibilities; among them are:
1. Both GnRH and ADH are released into the bloodstream to have their effects.
2. The targets of both substances are specified by receptors on particular cells.
3. Both substances are part of negative feedback loops.

Less major or less general:
1. Both these substances are peptides.
2. Both substances are released by neurons in the hypothalamus.

C. (3 points) There are many kinds of tumors, both cancerous and noncancerous, that can grow in or near the pituitary. Some of these tumors cause excessive production of hormones, whereas others restrict normal function in part of the pituitary. Name three places where a tumor might be located if your body stops producing ADH and oxytocin, but all other hormonal systems are normal.

1. In particular nuclei in the hypothalamus [where these hormones are produced].
2. In the pathway from the hypothalamus to the posterior pituitary [where the axons run that contain these hormones].
3. In the posterior pituitary [where the terminals of the hormone-producing axons are located].

2. (12 points total) The compound thapsigargin is extracted from *Thapsia garganica*, a plant commonly called the "deadly carrot". Thapsigargin is an inhibitor of the Ca\(^{++}\)-ATPase of the sarcoplasmic reticulum of both skeletal and cardiac muscle. It is a deadly poison.

A. (4 points) Predict the effects of thapsigargin on the first skeletal muscle twitch. Briefly explain.

The twitch will last longer and be larger because—depending on the dose of thapsigargin—the Ca\(^{++}\) released from the sarcoplasmic reticulum (SR) will take longer to be actively transported back into the SR or—if the dose is high enough—it cannot be transported back at all.

B. (4 points) Predict the effects of thapsigargin on the 100\(^{th}\) skeletal muscle twitch. Briefly explain.

After many twitches, the amount of Ca\(^{++}\) in the SR will be greatly depleted, so there will be little Ca\(^{++}\) to release by the 100\(^{th}\) activation; therefore, the 100\(^{th}\) twitch will be very much smaller than the first one.

[In fact, the cause of death by thapsigargin is suffocation because the muscles of breathing—the diaphragm and the thoracic muscles--cannot contract.]
C. (4 points) Fendiline is an L-type calcium channel blocker. Could Fendiline be used to treat thapsigargin poisoning? Briefly explain, citing any differences between the effects of the two drugs on heart and skeletal muscles.

Fendiline would not affect the DHPR receptor (DHPR) in skeletal muscles, because the DHPR does not form a Ca\(^{2+}\) channel in these muscles. This effect of Fendiline might be ambiguous from the information provided in the question; however, calling it "an L-type calcium channel blocker" does not give its mechanism. If an answer says that Fendiline does block the DHPR, then Fendiline could either cause suffocation on its own (by a complete block of the DHPR) or, if the Fendiline block of the DHPR receptor is partial, it could prolong the time for thapsigargin to deplete the Ca\(^{2+}\) from the SR. In this case, it would help somewhat, but the ultimate effect would be the same: suffocation from depletion of Ca\(^{2+}\) from the SR.

The effect on cardiac muscle is simpler: because much of the Ca\(^{2+}\) that triggers the cardiac muscle contraction enters by way of the L-type Ca\(^{2+}\) channel in the outer cell membrane, thapsigargin would initially increase the contraction (although not to the extent that it does in skeletal muscle), and the Fendiline would work to diminish this increase, so it is potentially a treatment for the effects of thapsigargin on the heart. [But you would die of suffocation, so the effect on the heart does little good!]
3. (15 points total) A scientist at UCSD studied the mechanism of **skeletal** muscle contraction. She isolated a muscle fiber and did a variety of experiments, each time causing the muscle to twitch by electrically stimulating it to produce a single action potential. For each experiment, plot Tension vs. Time.

A. (3 points) A single normal muscle twitch.

B. (3 points) Administered a DHP receptor inhibitor. Explain any differences from the normal twitch. With the DHP receptor blocked, no Ca\(^{++}\) will be released from the sarcoplasmic reticulum, so there will be no activation of the actin-myosin interactions, meaning that there will be no contraction.

C. (3 points) Administered a DHP receptor inhibitor while the muscle fiber is bathed in calcium. Explain any differences from the effect of the DHP inhibitor alone. Because no Ca\(^{++}\) enters from the extracellular fluid during a skeletal muscle twitch, having more external Ca\(^{++}\) will not help; there will still be no muscle contraction.

D. (3 points) Administered a Ca\(^{++}\)-ATPase inhibitor. Explain any differences from the normal twitch. This will stop the Ca\(^{++}\) from being removed from the actin-myosin, greatly prolonging the contraction.

E. (3 points) Removed the majority of the sarcoplasmic reticulum from the muscle fiber. Explain any differences from the normal twitch. This would remove the source of Ca\(^{++}\) for the actin-myosin, so there would be no contraction.
4. (8 points total) As a graduate student, you discover a drug (which you call “Gapnix”) that selectively blocks the gap junctions between smooth muscle cells. What effect would Gapnix have on:
   A. (4 points) Your ability to focus your vision? Briefly explain.
   Gapnix would have no effect. The muscles that control the lenses of your eyes are multi-unit, which have no gap junctions between them.
   B. (4 points) Your ability to pass food through your small intestine? Briefly explain.
   Gapnix would greatly slow down the passage of food through your small intestine because these smooth muscles are unitary. The synaptic inputs to these muscles are onto only a few of the fibers, which normally pass the electrical activity to the remaining fibers through gap junctions. With the gap junctions blocked, only a few of the fibers would be activated, so the contractions of these intestinal smooth muscles would be greatly weakened.

5. (12 points total) A cardiac disease called SQTS was first described in 2004. SQTS results from a mutation in the voltage-gated K⁺ channels in ventricular muscle fibers. This mutation causes voltage-gated K⁺ channels to activate faster and have a larger conductance than normal.
   A. (3 points) On the recording of the ventricular muscle action potential shown below, draw a dashed line showing how an action potential would be different in the muscle fibers with the mutated K⁺ channels.

   ![Ventricular Action Potentials](image)

   B. (3 points) On the line below the action potentials, draw a solid line to show what the ECG would look like from a person with the normal ventricular action potentials. Label the ECG components.

   ![ECG](image)

   C. (3 points) On the same ECG recording, draw a dashed line that shows what the ECG would look like in a person with SQTS. Explain any differences compared to the normal ECG.
   Because the ventricular muscle fibers repolarize faster—caused by the faster and more conductive K⁺ channels—the time between the QRS complex and the T wave is shorter, because the T wave is the repolarization of the ventricular action potentials.
   [In fact, SQTS stands for “Short Q-T Syndrome”.]

   D. (3 points) People die from SQTS because it can result in ventricular fibrillation. Explain how the abnormalities you have shown above could lead to ventricular fibrillation.
   The most likely cause for the fibrillation: because the individual ventricular muscle fibers have an unusually short action potential, they can fire an action potential before the next SA node-generated action potential reaches them, causing re-entry: the early-firing ventricular fibers initiate action potentials at abnormal sites, which with then cause contractions at several places in the ventricles at once. Once started, this pattern would keep the SA node-generated action potentials from controlling the ventricular beat, and the fibrillation would continue.
6. (12 points total) “Valvular insufficiency” is a condition of a heart valve: it cannot close completely during the cardiac cycle (i.e., it remains partially open during the time it would normally be shut). If the aortic valve is in this condition (called “Aortic insufficiency”):

A. (4 points) it produces a back-flow (also called “regurgitation”) of blood from the aorta to the ventricle during diastole. Briefly explain why.

Normally, the aortic valve would snap shut at the end of systole, as soon as the pressure in the aorta becomes higher than the pressure in the ventricle. (The aorta retains the pressure because its walls were stretched during systole.) In aortic insufficiency, the aortic valve cannot close completely, so the higher pressure in the aorta drives blood back into the left ventricle through the partially-open aortic valve.

B. (2 points) would there be a change in one or both of the heart sounds? If there is any change, briefly explain why.

The second heart sound (the “dub”) is likely to be weaker and more prolonged, as blood is squirted back into the ventricle for all of diastole.

C. (3 points) is the stroke volume abnormal? Briefly explain.

The path for ejecting blood during systole would be the same as normal, so the stroke volume (amount ejected during each contraction) would be at least normal. In fact, because the volume in the heart at the beginning of systole would be abnormally high (because the “regurgitated” blood would be added to the inflow from the atrium), the ventricular muscles would be stretched more than normal, so the muscles would contract more than usual (the Starling Law effect), and the stroke volume would be higher than normal.

D. (3 points) If this condition persists for many months, does it cause a change in the ECG compared to normal? If so, explain what changes; if nothing changes, explain why not.

Because the left ventricle would be consistently stretched by the regurgitated blood, the left ventricular muscle fibers would get larger. This can be detected as an enlargement of the R wave in lead I of the ECG and a reversal in sign of the R wave (i.e., a downward-going wave) in lead III.
7. (10 points total) The active component of the length-tension relationship for a muscle tells a great deal about its function.

A. (4 points) Describe how an active length-tension curve is generated.

A muscle is removed from an animal and stretched to different initial lengths while measuring the force needed to stretch it to that length. Single electrical shocks are delivered to the muscle and the amount of tension generated by the contraction is measured. The peak contraction (above the passive force required to bring the muscle to each length) is measured and plotted against the initial length of the muscle.

B. (4 points) Compare the active length-tension curves of skeletal and cardiac muscle fibers.

They are essentially identical: they both increase the amount of force they can generate above some minimal length, and show a maximal force at some length that is greater than the length ever achieved in the normal function of the muscle. If the muscle stretched beyond that point, the force generated by the muscle decreases, going to zero at some length that is about twice the normal rest length of the muscle.

C. (2 points) How would an active length-tension curve for smooth muscle in your intestinal tract differ from a length/tension curve for one of your skeletal muscles?

Such a length-tension curve would show many of the same features, except that the smooth muscle could generate force over a much greater variation in length.

8. (8 points total) Ivabridine is a selective blocker of If channels. Ivabridine is marketed as Procoralan to treat heart pain (this pain is called angina pectoris). Angina can have a number of different causes, such as lack of blood to the coronary vessels, a clot in a pulmonary artery, tachycardia, narrowing of the aortic valve (technical term: aortic stenosis), or inflammation of tissue around the heart or lungs

A. From your knowledge of If channels, how would Procoralan affect:

(a) (3 points) heart rate? Briefly explain.

It would slow down the heart rate because the time between heartbeats depends on the rate of activation of If in the SA node cells. If there are fewer If channels (which is what a blocker does—it binds to and inactivates target molecules), the rate of depolarization would decrease, prolonging the time between action potentials, which means that the heart rate decreases.

(b) (3 points) strength of cardiac muscle contraction? Briefly explain.

Procoralan would have no effect on the strength of contraction.

It is possible that the slowing of the heart will activate a reflex that increases sympathetic input onto the heart, which could—indirectly—increase muscle contraction strength. But this is beyond the scope of what we have considered so far, so it is not an expected answer.

B. (2 points) Based upon your answer to part A, what kind of problem that causes angina could be treated effectively with Procoralan? Briefly explain.

If the angina were caused by tachycardia (abnormally high heart rate), Procoralan could help to slow down the heart and relieve the angina.
9. (12 points total) For the following three groups of statements (A, B, and C), circle every letter that makes a TRUE statement. Note that any number of statements may be true—including none of them—so that if you do not circle a letter you are indicating that you believe that the statement is false. (You lose a point for every incorrect answer circled and for every correct answer not circled.)

A. Chemical communication is complex:
   a. hormones are chemicals secreted by a cell or group of cells into the blood for transport to a distant target, where they exert their physiological effects on distant targets.
   b. pheromones have been called “ectohormones” because they are chemicals produced by an animal within its body that acts on the outside of the animal’s body to produce its physiological effect.
   c. some substances that fit the definition for being a hormone are also used within the CNS as a neurotransmitter.
   d. many cytokines are not considered to be hormones because they have effects only locally, without being secreted into the circulatory system.

   \[a, c\]

B. Muscle disorders can have a variety of causes:
   a. in some types of muscular dystrophy, contractile fibers break down.
   b. an absence of enzymes may limit the availability of energy from the breakdown of glycogen.
   c. toxins produced by infectious diseases can disrupt the release of ACh at the NMJ.
   d. prolonged inactivity (as when a limb is immobilized in a cast) can lead to atrophy which, if prolonged, can be permanent.

   \[a, b, c, d\]

C. Smooth muscle differs from skeletal muscle:
   a. skeletal muscle can operate over a greater range of lengths.
   b. contractions in smooth muscles may be initiated by chemical signals without an action potential in the cells membrane.
   c. smooth muscle cells lack specialized postsynaptic regions.
   d. smooth muscle cells have less actin and myosin than striated muscle cells.

   \[b, c\]