NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Rhabdomyolysis: A Workout Breakdown

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Part I – Making up for Lost Time

Rachel, a 20-year-old student, usually started each day with a workout. The quiet hours before breakfast were the only opportunity she had to fit in some exercise. The rest of her days were filled with classes, studying, tutoring, and other activities. Her normal routine had changed the last few weeks. She had been staying up later than usual studying for midterm exams and she had been fighting lingering symptoms of the flu, so she had skipped workouts to keep up with her sleep.

Now that midterms had passed, and she had just rid herself of the stubborn virus, she was eager to get back to her regular morning workout, especially because she had signed up for an endurance event, the Mud Tougher, which was only three weeks away. Mud Tougher is a 12-mile race that includes obstacles, like climbing walls and traversing pools of water. The obstacles she could handle, but she rarely ran long distances, so she decided she would shift her workouts from upper body weight training in the gym to trail running. In order to make up for lost time, she decided to start with a week of seven-mile morning runs, then a second week of 10-mile morning runs, and a third week of 13-mile runs leading up to the event.

Rachel stepped out into the cool morning (10 °C/50 °F) with her running shoes laced tightly and mentally plotted a route that would be close to seven miles. Her university was located in a rural area with plenty of access to hiking trails, so she picked one that she was familiar with. The trail was about a mile away by road and consisted of a hilly five-mile loop, and a mile back. She did a short stretching routine then headed off down the road, pushing herself as hard as she could.

She returned from her run exhausted, hot, breathing heavy, and dripping with sweat in spite of the morning chill. Running for two hours on hilly trails felt more challenging than any leg workout she had done in the gym, and her legs felt weak. She was sitting in class later that afternoon when she noticed that her left and right quadriceps were beginning to ache. By dinnertime, the pain had severely escalated and continued through the night. In the morning, her legs were swollen and she struggled to get out of bed. She also felt nauseous and her urine had a brownish red color. Rachel asked a friend to drive her to the closest emergency room.

Questions

1. Given what you know about Rachel, what advice would you have given with respect to her running/training plan and preparing for the Mud Tougher?

2. What details of recent events in Rachel's life may have set her up for an injury?

3. What molecule is the primary energy source used by all cells to drive biochemical reactions?

Part II – Powering Skeletal Muscle Cell Contraction

It makes perfect sense that the contraction of a skeletal muscle is an active process, and that it requires energy. The cellular basis of skeletal muscle contraction depends on a steady supply of intracellular adenosine triphosphate (ATP) to fuel the sliding of thick (myosin) filaments along thin (actin) filaments within sarcomeres. ATP provides energy when a phosphate group is removed via hydrolysis, leaving adenosine diphosphate (ADP), a favorable reaction that releases energy that can be used by some enzymes, like myosin, to do work.

Perhaps less intuitively, the relaxation of muscle at the cellular level is also an active process. In relaxed skeletal muscle, actin and myosin interactions are blocked by troponin and tropomyosin. Troponin and tropomyosin are only positioned to block actin and myosin interactions when cytosolic Ca^{2+} is low. Removing Ca^{2+} from the cytosol requires ATP-dependent pumps (Figure 1). At resting membrane potential, the Na^+/K^+-ATPase (NKA), also called the sodium potassium pump, exports three Na^+ from the cell and imports two K^+ into the cell for each molecule of ATP that is hydrolyzed to ADP. A Na^+/Ca^{2+} exchanger (NCX) uses a high concentration of Na^+ in the interstitial fluid to drive the exchange of three extracellular Na^+ for each Ca^{2+} that is transported out of the cell. If the concentration of Na^+ in the cytosol is abnormally high, the transport properties of NCX may be reversed. Ca^{2+} is also removed from the cytosol by the sarco(endo)plasmic reticulum Ca^{2+}-ATPase (SERCA). SERCA transports two Ca^{2+} from the cytosol into the sarcoplasmic reticulum for each molecule of hydrolyzed ATP. In a stimulated skeletal muscle cell, Ca^{2+} floods from the sarcoplasmic reticulum into the cytosol. This allows myosin to bind to, and slide along actin, powered by ATP and causing contraction of sarcomeres, and by extension, skeletal muscle cells. If cytosolic Ca^{2+} levels increase too much (by an order of magnitude) for too long, Ca^{2+}-dependent proteases and lipases may be more active than usual, leading to destruction of cellular proteins and membranes and inducing apoptosis.

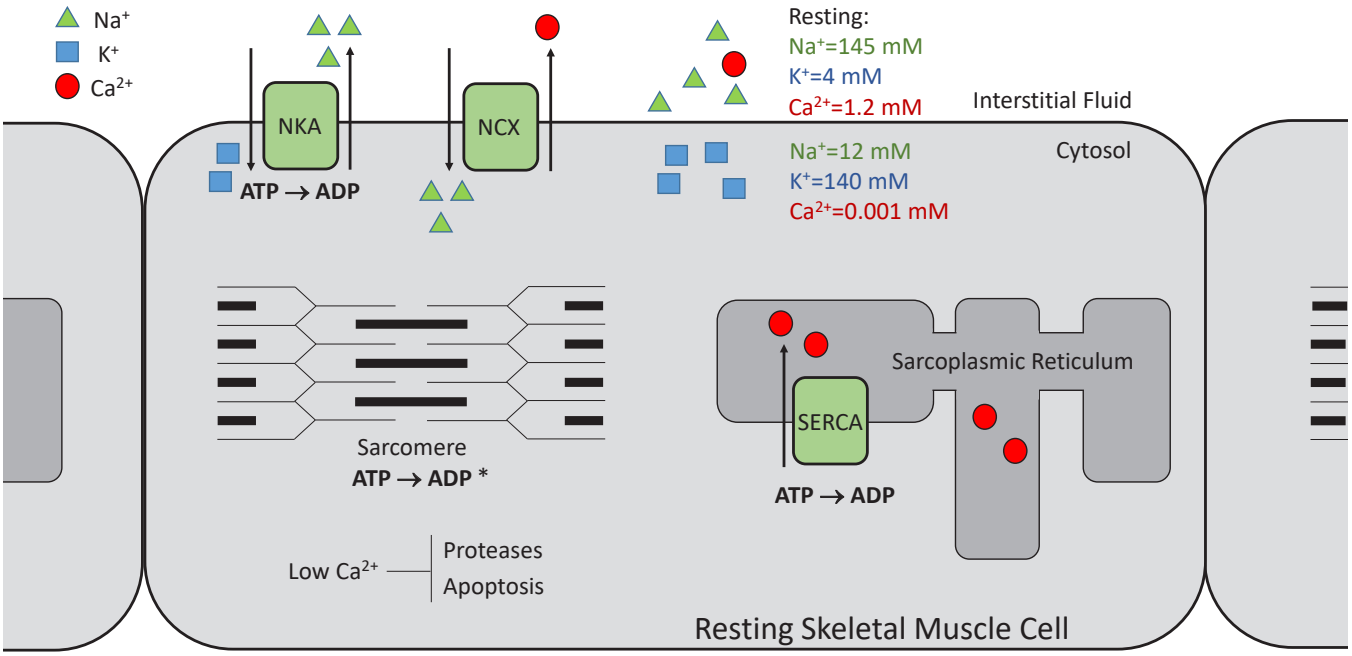

Figure 1. Model of Ca^{2+} transport in a resting skeletal muscle cell. The Na^+/K^+-ATPase (NKA) transports two K^+ into the cytosol and three Na^+ out of the cell for each molecule of ATP hydrolyzed. High extracellular concentration of Na^+ drives an exchange of three extracellular Na^+ for one intracellular Ca^{2+} through the Na^+/Ca^{2+}-exchanger (NCX). The sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) transports two Ca^{2+} into the sarcoplasmic reticulum for each molecule of ATP hydrolyzed. Together these three ion transporters help to establish an ion gradient in a resting skeletal muscle cell across the plasma membrane; interstitial fluid 145 mM Na^+; 4 mM K^+ ; 1.2 mM Ca^{2+}; cytosol 12 mM Na^+ ; 140 mM K^+ ; 0.001 mM Ca^{2+}. Low cytosolic Ca^{2+} in a resting muscle cell attenuates protease and lipase activity; abnormally high cytosolic Ca^{2+} may lead to increased protease and lipase activity, damaging cellular components and membranes, and inducing apoptosis. ATP-dependent processes are indicated by ATP→ADP (* in stimulated muscle cells).

Skeletal muscle cells are uniquely adapted to meet high demands for ATP and quickly renew depleted pools. Some muscle cells, particularly those of oxidative fibers, are rich in a protein called myoglobin that binds to oxygen and stores it so it is readily available for the generation of new ATP by aerobic cellular respiration. Creatine phosphate is a molecule that is abundant in muscle cells; it contains a phosphate group that can be quickly donated to adenosine diphosphate (ADP) by creatine kinase (CK) to renew pools of depleted ATP. The skeletal muscle cells of athletes may be particularly well-adapted to strenuous activity by increasing the abundance of these proteins. These mechanisms allow skeletal muscle cells to quickly generate ATP to engage in extended bouts of physical activity, powering myosin and regulating skeletal muscle cell cytosolic concentrations.

Questions

1. If a skeletal muscle cell has depleted its stores of ATP how will the altered transport properties of the following transporters affect cytosolic ion concentrations (increase, decrease, no change) relative to normal?

Skeletal Muscle Cell With Depleted ATP Stores			
Ion Transporter	*Cytosolic K^+*	*Cytosolic Na^+*	*Cytosolic Ca^{2+}*
NKA			
NCX			
SERCA			

2. How would the changes from the table above result in skeletal muscle cell protease and lipase activity and the potential for apoptosis?

3. If there was a dramatic increase in skeletal muscle cell damage and apoptosis, what would you expect to happen to levels of myoglobin and CK in the blood?

Part III – Crisis in the Clinic

When Rachel arrived at the emergency room her vital signs were listed as: blood pressure 120/57 mm Hg, heart rate 70 BPM, 17 breath/min, and temperature was 36.8 ˚C / 98.2 ˚F. The physician, Dr. Maria González, ordered a panel of blood tests after reviewing Rachel's vital signs, symptoms, and patient history. Dr. González was concerned that the cause of her symptoms was rhabdomyolysis, the destruction of skeletal muscle cells, which has a wide range of causes including trauma (crush syndrome), genetics, viral infection, and extended physical exertion. The results of the blood test indicated that Rachel had exercise-induced rhabdomyolysis (ex-RML) and that her condition was critical and had to be quickly addressed (Table 1). Her kidneys were struggling because of her low blood pressure resulting from hypovolemia, as fluids moved from her plasma into damaged regions of skeletal muscle. The kidney tubules may have been damaged by high levels of plasma myoglobin and CK, and as a result her body was not clearing creatinine or properly balancing plasma ions by conserving them or excreting them in the urine. Plasma ion imbalance can lead to severe neurologic and cardiac complications (e.g., arrhythmia). Dr. González placed Rachel on intravenous (IV) normal saline solution with an initial fluid rate of 5 L/day to restore blood volume with a goal urine output of 200–300 mL/hr and blood values were recorded every six hours (Figure 2, next page).

Table 1. Patient and reference vital signs and blood plasma values. Venous blood plasma values were assayed directly after admittance. Values are provided for each parameter along with normal reference values.

Vital Signs		
Parameter	*Patient Value*	*Reference Range*
Blood pressure	120/57 mm Hg	130/80–90/60 mm Hg
Heart rate	70 bpm	60–100 bpm
Breathing rate	17 breaths/min	12–20 breaths/min
Body temperature	98.2 ˚F	97–99 ˚F
Venous Blood Values		
Na^+	135 mEq/L	135–145 mEq/L
K^+	7.0 mEq/L	3.5–5.0 mEq/L
Ca^{2+}	1.2 mEq/L	1.1–1.3 mEq/L
Cl^-	101 mEq/L	95–105 mEq/L
HCO_3^-	23 mEq/L	18–23 mEq/L
Creatinine	4.0 mg/dL	(female) 0.6–1.0 mg/dL
Creatine Kinase (CK)	45,000 U/L	(female) 24–140 U/L

Questions

1. Which of the initial vital signs and blood values were out of range?

2. What specific changes in Rachel's muscle cells and kidney function are leading to elevated plasma K^+ levels?

3. After 30 hours, according to the data in Figure 2, would you increase or decrease the normal saline IV fluid rate? Why?

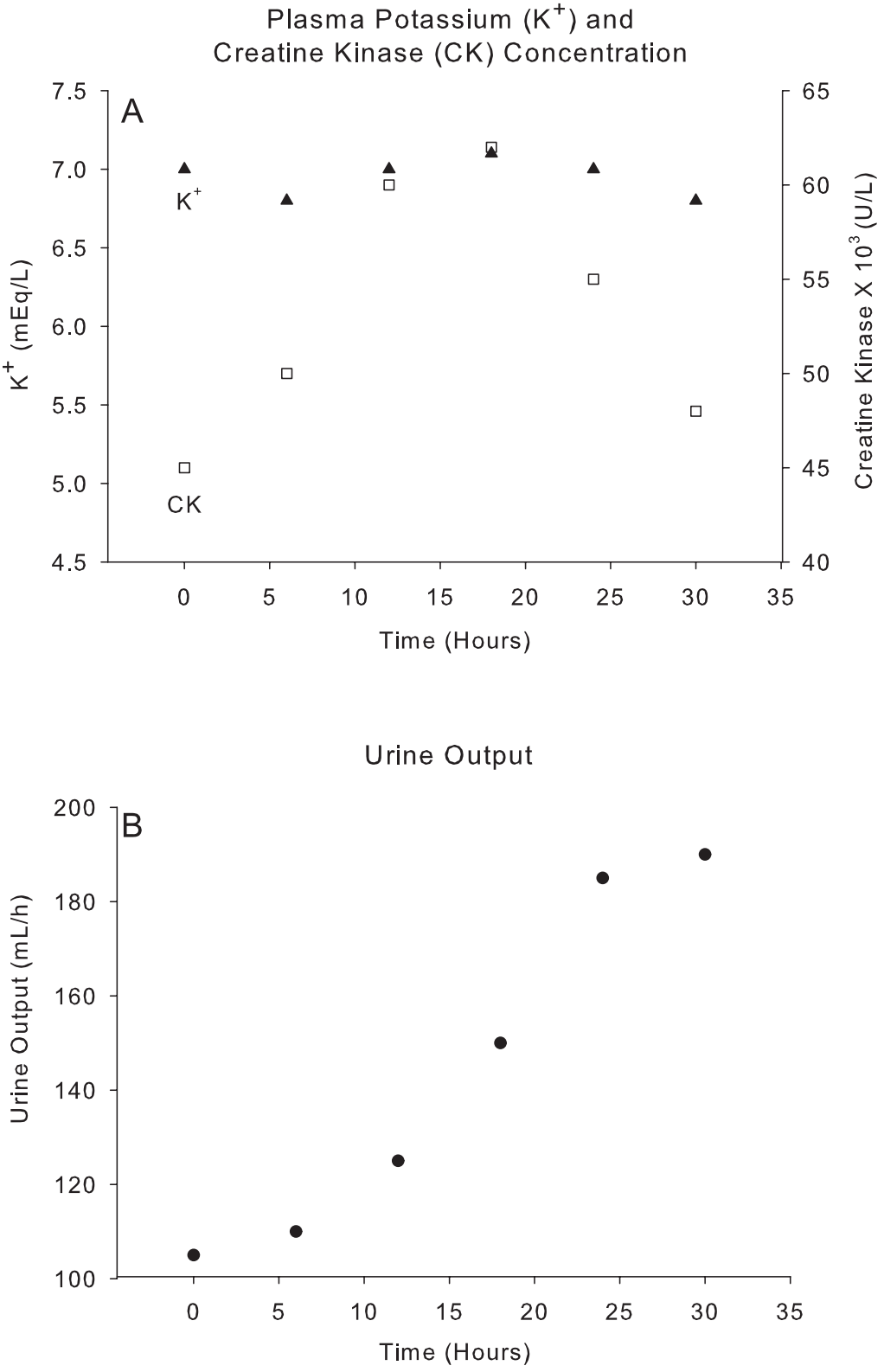

Figure 2. Patient blood plasma potassium (K^+) and creatine kinase (CK) concentration, and urine output, over time. K^+ (filled triangles) and CK (open squares) were measured every six hours after the patient was admitted (A). Urine output (filled circles) was measured every six hours after the patient was admitted (B).

Part IV – Rest, Relaxation, and Recovery

After several more days of supportive IV fluid treatment, Rachel's condition began to improve. Her K^+ levels dropped to 4.5 (mEq/L) and CK to 6,000 (U/L), and Dr. González felt that she was ready to go home. She was instructed to drink a lot of fluids and ... relax! Although Rachel would make a full recovery, it would take time to heal. She would need to be more cautious with her training in the future. Her goals for the Mud Tougher were ambitious, but attainable; the problem stemmed from pushing herself too hard, too quickly. It takes time (weeks or months) for skeletal muscle cells to adapt to new demands, in part by upregulating levels of myoglobin and CK. Unconditioned muscles are particularly susceptible to eccentric contractions, when contracting muscles lengthen, as experienced during weight lifting or running downhill. Rachel would not necessarily have to change her target goals, but she would have to reconsider the path she would take to achieve them.

Questions

1. Summarize the risk factors for exRML.

2. Do these risk factors apply to you or anyone you know?