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Chapter 1 Costanzo: lecture 1-7

BOX 1.1 Clinical Physiology: Glucosuria Due to Diabetes Mellitus

DESCRIPTION OF CASE. At his annual physical examination, a 14-year-old boy reports symptoms of frequent urination and severe thirst. A dipstick test of his urine shows elevated levels of glucose. The physician orders a glucose tolerance test, which indicates that the boy has type I diabetes mellitus. He is treated with insulin by injection, and his dipstick test is subsequently normal.

EXPLANATION OF CASE. Although type I diabetes mellitus is a complex disease, this discussion is limited to the symptom of frequent urination and the finding of glucosuria (glucose in the urine). Glucose is normally handled by the kidney in the following manner: Glucose in the blood is filtered across the glomerular capillaries. The epithelial cells, which line the renal proximal tubule, then reabsorb all of the filtered glucose so that no glucose is excreted in the urine. Thus a normal dipstick test would show no glucose in the urine. If the epithelial cells in the proximal tubule do not reabsorb all of the filtered glucose back into the blood, the glucose that escapes reabsorption is excreted. The cellular mechanism for this glucose reabsorption is the Na^+-glucose cotransporter in the luminal membrane of the proximal tubule cells. Because this is a carrier-mediated transporter, there is a finite number of binding sites for glucose. Once these binding sites are fully occupied, saturation of transport occurs (transport maximum).

In this patient with type I diabetes mellitus, the hormone insulin is not produced in sufficient amounts by the pancreatic β cells. Insulin is required for normal uptake of glucose into liver, muscle, and other cells. Without insulin, the blood glucose concentration increases because glucose is not taken up by the cells. When the blood glucose concentration increases to high levels, more glucose is filtered by the renal glomeruli and the amount of glucose filtered exceeds the capacity of the Na^+-glucose cotransporter. The glucose that cannot be reabsorbed because of saturation of this transporter is then "spilled" in the urine.

TREATMENT. Treatment of the patient with type I diabetes mellitus consists of administering exogenous insulin by injection. Whether secreted normally from the pancreatic β cells or administered by injection, insulin lowers the blood glucose concentration by promoting glucose uptake into cells. When this patient received insulin, his blood glucose concentration was reduced; thus the amount of glucose filtered was reduced, and the Na^+-glucose cotransporters were no longer saturated. All of the filtered glucose could be reabsorbed, and therefore no glucose was excreted, or "spilled," in the urine.

BOX 1.2 Clinical Physiology: Hyposmolarity With Brain Swelling

DESCRIPTION OF CASE. A 72-year-old man was diagnosed recently with oat cell carcinoma of the lung. He tried to stay busy with consulting work, but the disease sapped his energy. One evening, his wife noticed that he seemed confused and lethargic, and suddenly he suffered a grand mal seizure. In the emergency department, his plasma Na^+ concentration was 113 mEq/L (normal, 140 mEq/L) and his plasma osmolarity was 230 mOsm/L (normal, 290 mOsm/L). He was treated immediately with an infusion of hypertonic NaCl and was released from the hospital a few days later, with strict instructions to limit his water intake.

EXPLANATION OF CASE. The man's oat cell carcinoma autonomously secretes antidiuretic hormone (ADH), which causes syndrome of inappropriate antidiuretic hormone (SIADH). In SIADH, the high circulating levels of ADH cause excessive water reabsorption by the principal cells of the late distal tubule and collecting ducts. The excess water that is reabsorbed and retained in the body dilutes the Na^+ concentration and osmolarity of the ECF. The decreased osmolarity means there is also decreased effective osmotic pressure of ECF and, briefly, osmotic pressure of ECF is less than osmotic pressure of ICF. The effective osmotic pressure difference across cell membranes causes osmotic water flow from ECF to ICF, which results in cell swelling. Because the brain is contained in a fixed structure (the skull), swelling of brain cells can cause seizure.

TREATMENT. Treatment of the patient with hypertonic NaCl infusion was designed to quickly raise his ECF osmolarity and osmotic pressure, which would eliminate the effective osmotic pressure difference across the brain cell membranes and stop osmotic water flow and brain cell swelling.

BOX 1.4 Clinical Physiology: Multiple Sclerosis

DESCRIPTION OF CASE. A 32-year-old woman had her first episode of blurred vision 5 years ago. She had trouble reading the newspaper and the fine print on labels. Her vision returned to normal on its own, but 10 months later, the blurred vision recurred, this time with other symptoms including double vision, and a "pins and needles" feeling and severe weakness in her legs. She was too weak to walk even a single flight of stairs. She was referred to a neurologist, who ordered a series of tests. Magnetic Resonance Imaging (MRI) of the brain showed lesions typical of multiple sclerosis. Visual evoked potentials had a prolonged latency that was consistent with decreased nerve conduction velocity. Since the diagnosis, she has had two relapses and she is currently being treated with interferon beta.

EXPLANATION OF CASE. Action potentials are propagated along nerve fibers by spread of local currents as follows: When an action potential occurs, the inward current of the upstroke of the action potential depolarizes the membrane at that site and reverses the polarity (i.e., that site briefly becomes inside positive). The depolarization then spreads to adjacent sites along the nerve fiber by local current flow. Importantly, if these local currents depolarize an adjacent region to threshold, it will fire an action potential (i.e., the action potential will be propagated). The speed of propagation of the action potential is called conduction velocity. The further local currents can spread without decay (expressed as the length constant), the faster the conduction velocity. There are two main factors that increase length constant and therefore increase conduction velocity in nerves: increased nerve diameter and myelination.

Myelin is an insulator of axons that increases membrane resistance and decreases membrane capacitance. By increasing membrane resistance, current is forced to flow down the axon interior and less current is lost across the cell membrane (increasing length constant); because more current flows down the axon, conduction velocity is increased. By decreasing membrane capacitance, local currents depolarize the membrane more rapidly, which also increases conduction velocity. In order for action potentials to be conducted in myelinated nerves, there must be periodic breaks in the myelin sheath (at the nodes of Ranvier), where there is a concentration of Na^+ and K^+ channels. Thus at the nodes, the ionic currents necessary for the action potential can flow across the membrane (e.g., the inward Na^+ current necessary for the upstroke of the action potential). Between nodes, membrane resistance is very high and current is forced to flow rapidly down the nerve axon to the next node, where the next action potential can be generated. Thus the action potential appears to "jump" from one node of Ranvier to the next. This is called saltatory conduction.

Multiple sclerosis is the most common demyelinating disease of the central nervous system. Loss of the myelin sheath around nerves causes a decrease in membrane resistance, which means that current "leaks out" across the membrane during conduction of local currents. For this reason, local currents decay more rapidly as they flow down the axon (decreased length constant) and, because of this decay, may be insufficient to generate an action potential when they reach the next node of Ranvier.

Challenge Yourself

Answer each question with a word, phrase, sentence, or numerical solution. When a list of possible answers is supplied with the question, one, more than one, or none of the choices may be correct. Correct answers are provided at the end of the book.

1 *Solution A contains 100 mM NaCl, Solution B contains 10 mM NaCl, and the membrane separating them is permeable to Cl^- but not Na^+. What is the orientation of the potential difference that will be established across the membrane?*

2 *The osmolarity of a solution of 50 mmol/L $CaCl_2$ is closest to the osmolarity of which of the following: 50 mmol/L NaCl, 100 mmol/L urea, 150 mmol/L NaCl, or 150 mmol/L urea?*

3 *How does the intracellular Na^+ concentration change following inhibition of Na^+-K^+ ATPase?*

4 *Which phase of the nerve action potential is responsible for propagation of the action potential to neighboring sites?*

10 *Solution A contains 10 mmol/L glucose, and Solution B contains 1 mmol/L glucose. If the glucose concentration in both solutions is doubled, by how much will the flux (flow) of glucose between the two solutions change (e.g., halve, remain unchanged, double, triple, quadruple)?*

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1 Solution B, negative; or Solution A, positive

2 150 mmol/L urea

3 Increases

4 Upstroke of the action potential

10 Double (Hint: $\Delta C = 10 - 1 = 9$. If both sides doubled, $\Delta C = 20 - 2 = 18$.)