NATIONAL CENTER FOR CASE STUDY TEACHING IN SCIENCE

Liam's Head Injury:

Is This the Cause of His Frequent Urination?

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Liam has recently suffered a head injury when he fell while skateboarding. Subsequently he has noticed that he is constantly thirsty, that he needs to urinate more frequently, and that his overall urine output is greater than before. Is the head injury associated with his new symptoms? Can he be treated? Answer the questions below after viewing the following video in which Liam meets with healthcare professionals at a local hospital to learn the cause and treatment for his condition: <https://youtu.be/KMtyTy81FDs>.

Vocabulary

Osmolarity: the number of osmoles of a solute per liter of solution. To calculate osmolarity, you need to consider the number of moles of a substance per liter of solution and whether the substance dissociates when in solution. Thus a 1 M solution of glucose has an osmolarity of 1 Osm/L, while a 1 M solution of NaCl has an osmolarity of 2 Osm/L.

Osmolality: the number of osmoles of a solute per kg of water. This term is more common in clinical settings and is used in the video and in some of the questions.

Intracellular fluid compartment: the fluid that is found inside all the cells in the body including blood cells.

Extracellular fluid compartment: the fluid in the body that is outside cells (this includes both the plasma and interstitial fluid) but excludes, for example, fluid in the lumen of the gastrointestinal tract.

Interstitial fluid compartment: the fluid that bathes the cells of the tissues (excluding plasma).

Pathological: associated with a disease or disorder

Questions – Physiology

1. Where is vasopressin (also known as antidiuretic hormone (ADH)) produced, where is it released from, and what stimulates its release?
2. What are the physiological roles of vasopressin? (Include both the overall function and the specific mechanism.)
3. What is the name for the condition that Liam has? Explain why, after his head injury, Liam starts to produce very large volumes of dilute urine.
4. Explain how Liam's body attempts to compensate for this excessive water loss.
5. Initially during the fluid deprivation test, Liam was not allowed to eat or drink anything. Predict what would happen to his plasma osmolarity and blood pressure during this time.

6. The nurse will stop a fluid deprivation test if the patient's weight drops by more than 3%, which indicates a deficiency in the ability to conserve body water. In a 70 kg individual with this deficiency, this would represent about 2 L of water loss. Predict the changes to the osmolarity of the extracellular, intracellular, and interstitial fluid in this individual. Further, describe the movement of water between these compartments. Why is it important to halt the test?

7. Halfway through the fluid deprivation test, Liam is injected with vasopressin and is given some water to drink. Predict what would happen to his plasma osmolarity and rate of urine production. Explain your answer including the cellular mechanism underlying the effect of vasopressin on the kidney.

8. In the video, Dr. Scholey asks Liam whether there is a history of mental illness in his family to help rule out the possibility that he has a condition called psychogenic diabetes insipidus, in which individuals drink abnormally high volumes of fluid even though their vasopressin system is intact. What would you expect to occur in these individuals in terms of circulating levels of vasopressin and urine osmolarity and volume?

9. How would urine osmolarity and volume change over time during the fluid deprivation test in individuals with psychogenic diabetes insipidus as they are deprived of fluids? (Assume that this is before the injection of vasopressin.)

10. Another type of diabetes insipidus, termed nephrogenic diabetes insipidus, is found in individuals with mutations to vasopressin receptor 2 causing a loss of receptor function. How would individuals with nephrogenic diabetes insipidus be similar to and differ from those with central diabetes insipidus?

11. Refer to the figure below showing the results from a fluid deprivation test of three individuals:

    Individual 1: normal vasopressin production/secretion and vasopressin receptor activity

    Individual 2: complete nephrogenic diabetes insipidus

    Individual 3: complete central diabetes insipidus

    Match the individuals above (numbers) with the expected results (letters on the figure) and explain your response.

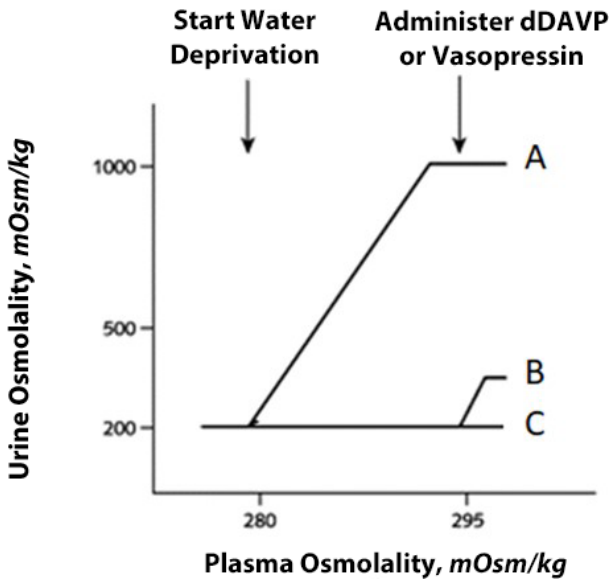

Figure 1. Changes in plasma and urine osmolality in three individuals during a fluid deprivation test. Figure modified from: Sands & Bichet, 2006.

Questions – Cellular and Molecular Biology

12. In the case study video, we learn that the release of vasopressin is impaired in Liam due to a head injury. The amino acid sequence of vasopressin is similar to another hormone found in the body called oxytocin (see Figure 2). Oxytocin is released from the posterior pituitary and stimulates uterine contractions during labor and is needed for lactation.

Figure 2. Amino acid sequences of vasopressin and oxytocin.

    a. What does the large bracket connecting two of the amino acid residues in each neuropeptide represent?
    b. When researchers were developing the drug desmopressin that the pharmacist prescribed to Liam, they would have noted differences in which part or parts of these two neuropeptide sequences?

13. Neuropeptide hormones such as vasopressin must interact with cell receptors to exert their action(s) on the body.
    a. Given the similarity of the amino acid sequences for vasopressin and oxytocin, which characteristics would you predict to be the most important for recognition by their receptor(s)?
    b. Which position in the amino acid sequence differs the most between the two hormones? (*Hint:* review properties of individual amino acids.)
    c. Given the characteristics of the amino acid residue at position 8 in vasopressin, what type of amino acids would you expect to find in the portion of the cell membrane receptor that could maximize the hormone binding interaction with its receptor? (*Hint:* think about properties of the R groups of various classes of amino acids).

14. Vasopressin binds to vasopressin receptors (specifically V2 receptors or V2R) in the plasma membrane of the distal convoluted tubule and collecting duct of the kidney to regulate water reabsorption and urine concentration. Vasopressin also acts on two other types of vasopressin receptors to increase blood pressure under extreme blood loss (V1AR receptors) and to regulate adrenocorticotropin hormone secretion (V1BR, also known as V3R receptors). All three of these receptor types belong to a single class of plasma membrane receptors known as G-protein-coupled receptors (GPCRs). What are three common characteristics of GPCRs?

15. List the intracellular signaling events that take place upon binding of vasopressin to its G-protein coupled receptor and ending in the increase in membrane permeability of the cells of the distal convoluted tubule and collecting duct.

16. To increase its half-life in the body, desmopressin was designed to avoid recognition by enzymes that might degrade it. One strategy that turned out to be very effective was to use D-arginine at position 8 in the neuropeptide. Are you surprised that this was effective? Why or why not?

17. We learn in the video that Liam has central diabetes insipidus caused by a head injury with a resulting loss of vasopressin release, but nephrogenic diabetes insipidus can result from loss-of-function mutations in the V2R vasopressin receptor (other cases are caused by mutations in aquaporin 2). In the case of the V2R receptor, in addition to frameshift or nonsense mutations in the V2R gene, what sort of changes would result in nephrogenic diabetes insipidus?