MEDICAL EDUCATION

Untangle the *Convoluted NOTs*: Learning Renal Physiology

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Abstract

Using definite, negative statements (the NOTs) can help reinforce and strengthen students' conception of physiology. A NOT statement implies that there is always the expected homeostatic response or compensatory mechanism that will be observed when the body is challenged and fluctuations occur. These NOT sentences highlight the built-in design, homeostatically wired in integrated physiology. Examples using this "untangle the NOT" teaching and learning approach in renal system are given here. We also created a character, a Japanese medical student, named Miss Take (pun on mistake) to illustrate some of the common misconceptions in understanding renal physiology.

Keywords: Concept, Learning, Negative statements, Renal physiology.

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Introduction

Making definite negative statements (NOTs) can be useful to define and clarify thinking when learning physiology.

Below are 14 "negative" samples of the NOTs to take note in renal physiology!

1. Glomerular Hydrostatic Pressure does *Not* Decrease Much along the Capillary.

Glomerular filtration rate (GFR) is determined by the net filtration pressure (NFP) and the filtration coefficient. The NFP is in turn the net pressure between the three starling forces, namely glomerular oncotic, glomerular hydrostatic, and Bowman capsular hydrostatic pressures. It is the NFP that progressively decreases along the length of the glomerulus from the afferent to the efferent arteriolar end. In the kidneys that filter 125 mL/min (180 liters/day), the glomerular hydrostatic pressure is higher (around 50–60 mm Hg) than that in other tissue capillaries. In addition, as the glomerulus is sandwiched between two high-resistance renal arterioles, the glomerular hydrostatic pressure is only slightly reduced along the capillary and this obviously serves the important function of sustaining a high GFR.

2. Glomerular Oncotic Pressure does *Not* Remain the Same along the Capillary.

The filtration fraction at the glomerular capillary is a significant 20%. Filtration fraction is the proportion of the total renal plasma flow (RPF) that is filtered or GFR/RPF. The plasma proteins that are basically non-filterable become concentrated along the glomerulus as the plasma water is filtered into the Bowman capsular space. Thus, the oncotic pressure that is due to the plasma protein concentration rises along the glomerulus from 25 mm Hg at the afferent arteriolar to about 40 mm Hg near the efferent arteriolar end (Fig. 1). Thus in calculating the NFP, an average value or mean glomerular oncotic pressure is used.

It should be pointed out that the proportionate change in GFR that accompanies a change in renal blood flow (RBF) is predominant due to the inverse change in the mean oncotic pressure in the glomerulus. For example, a vasoconstrictor that reduces RBF leads to a corresponding decrease in GFR by lowering the NFP through an inverse effect in increasing the mean oncotic pressure in the glomerular capillary.

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3. Renal Autoregulation is *Not* the Maintenance of Renal Blood Pressure.

Physiology definitions (I coined the term "DePHYnation") are essential to describe physiology accurately. The renal autoregulation of RBF also autoregulates GFR. Autoregualtion of GFR will then control the filtered solute load given by GFR x P#, where P# is the plasma concentration of filterable solute #. As in the cerebral and coronary vasculatures, autoregualtion of blood flow is the maintenance of a relatively constant organ perfusion over a certain physiological range of blood pressure fluctuations.

Fig. 1: Miss Take and glomerular oncotic pressure

Renal autoregulation of RBF/GFR is an intrinsic mechanism, independent of extrinsic neural input or action of circulating endocrine hormones. The two concurrent operating intrinsic pathways are named myogenic and the tubulo-glomerular (t–g) feedback mechanisms.

4. Renal Autoregulation is *Not* due to the Action of Renin.

The renin enzymatic hormone is always released by the kidneys in response to extracellular fluid (ECF) and blood volume reduction. ECF volume changes reflect changes in the sodium balance. Hypovolemia or negative sodium balance will trigger the secretion of renal renin via three pathways namely baroreflex renal sympathetic activity, intrarenal baroreceptor sensing, and a paracrine stimulus from the distal tubular macula densa.

That said, the macula densa has a separate paracrine signal (vasoactive on the afferent arteriole) that is involved in the t–g feedback of renal autoregulation of RBF/GFR. The two paracrines from the macula densa are differently involved either in renin secretion for sodium balance control or vasoconstrictor/vasodilator secretion for RBF/GFR autoregulation (Fig. 2).

5. Renin is *Not* Released from the Macula Densa.

The common confusion among students is between the juxtaglomerular apparatus (JGA) and the JG cells of the afferent arteriole. The JGA comprises the distal tubular macula densa and the pre-glomerular afferent arteriole.

Renin secretion is released or inhibited from the afferent arteriolar granular JG cells by paracrines from the macula densa.

6. Renal Autoregulation is *Not* Evident *in vivo* when the Blood Pressure Drops to 80 mm Hg.

The text book description of renal autoregualtion of RBF/GFR is from *in vitro* experiments on denervated kidneys. In the absence of renal sympathetic input, the intrinsic mechanisms within the renal tissues (myogenic/macula densa mechanisms) function to sustain a relatively constant renal perfusion when the perfusing pressure fluctuates over a certain range.[1]

However, *in vivo*, in the integrated whole-body homeostasis, the extrinsic renal sympathetic response to hypovolemia predominates and takes priority over the intrinsic renal autoregulation of RBF/GFR. In hypovolemia, renal sympathetic vasoconstriction of renal arterioles will affect a temporary reduction in RBF/GFR as a part of compensation to restore sodium balance and ECF/blood volume. Thus even though the hypovolemia may be associated with a lower blood pressure of 80 mm Hg (still in the operating range of the *in vitro* autoregulating experimental data), real blood flow will be decreased. The intrinsic autoregulation is masked by the renal sympathetic activity. Renal sympathetic nerve, in hypovolemia always reduces sodium urinary excretion through a three-prong action; reduced filtered sodium load, increases tubular reabsorption directly and also via stimulating renin release from the afferent arteriolar JG cells.

7. The Renal Plasma Threshold for Glucose does *Not* Change even after "All the Cakes You can Eat" at Secret Recipe!

In a person with normal pancreatic function, the post-prandial hyperglycemia will produce a rapid response from the pancreas to release the anabolic hormone insulin as well as inhibiting the counter regulatory catabolic hormone glucagon.

The plasma glucose concentration is unlikely to exceed the renal plasma threshold for glucose when the filtered glucose load will overwhelm the proximal convoluted tubular capacity for reabsorbing glucose.

All the filtered load will be reabsorbed.

Even in diabetes mellitus of recent occurrence, when the regular hyperglycemia has not affected glomerular filtration barrier, the renal plasma threshold for glucose is unchanged. Glucosuria is found when the filtered glucose load (GFR x plasma glucose concentration) exceeds the maximum tubular reabsorption rate for glucose.

8. After Drinking a Large Amount of Water in a Short Time, the Resulting Hyponatremia does *Not* Stimulate Aldosterone Secretion.

The water drinking produces a positive water balance with hypo-osmolarity of the plasma (hyponatremia). As the total body sodium or sodium balance is unchanged, the physiological homeostatic response will be to excrete the excess water and not to add sodium to the body.[2] You do not have to lose sodium to become hyponatremic. So the appropriate compensation will be inhibition of the hypothalamic osmoreceptor/antidiuretic hormone (ADH) mechanism. A water diuresis takes place.

If the hyponatremia in this normal case of positive water balance stimulates directly or indirectly via renin, an increase in aldosterone level, an illogical consequence, positive sodium balance will result (Fig. 3).

Fig. 2: Miss Take and renin

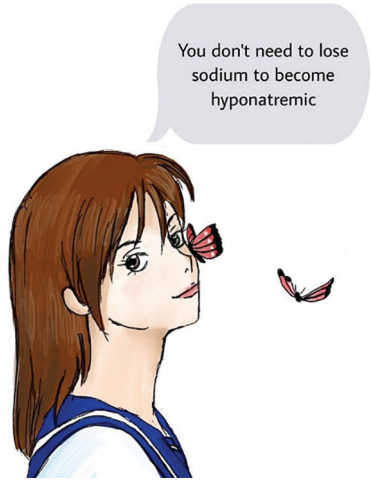

Fig. 3: Miss Take and positive water balance

9. Sweat is Always *Not* Hypertonic.

The intracellular fluid (ICF) volume is twice the ECF space. The ICF can serve as a water reservoir to provide fluid when the ECF volume is reduced. When hypotonic sweat is lost, the ECF is hypertonically contracted. There will be a compensatory shift or efflux of fluid from the ICF to the ECF. So if an original 500 mL of sweat was perspired, the actual reduction of ECF will be less than 500 mL with the provision of some osmotic ICF movement to ECF. Check this out: there is evidence that trained athletes produce a more hypotonic sweat. This means the resulting hyperosmolarity of the ECF will be greater. The compensatory osmotic efflux of water from the ICF to ECF will then also be higher.

10. Sodium and Water are Always *Not* Secreted by the Renal Tubules.

In renal handling of solutes and water, secretion is in the direction from the peritubular capillary, either transepithelially or paracellularly or both pathways into the luminal fluid. Water is only reabsorbed transcellularly via aquaporins or paracellularly through the intercellular tight junctions. The high GFR (180 liters daily) is markedly reduced to a urine output of about 2 liters/day. There is no need and no tubular water secretion (Fig. 4).

The sodium cation is also only reabsorbed, mainly transcellularly.[3] The first step, sodium entry at the luminal membrane can occur at different nephron segments by solute-linked secondary transport or sodium channels. The second step that completes sodium reabsorption all involves the same active Na/K ATPase at the basolateral side of the tubular cells. Sodium is extruded into the interstitial fluid and enters the peritubular capillary.

11. The Clearance of Glucose is *Not* Zero mg/mL.

The units of parameters are important to take note of. The word "clearance" can give the idea that a certain amount of the solute is cleared in the urine. The renal clearance concept actually refers to the imaginary volume of plasma that has been cleared of that solute that is found in the urine. So for glucose that is filtered and completely recycled back into the blood, no theoretical volume of plasma has been cleared of glucose. The glucose renal clearance is zero volume (of plasma) per time (mL/min).

Fig. 4: Miss Take and renal water handling

12. The Glomerulo-tubular (G–T) Balance is *Not* Evident When the ECF Volume Changes.

The G–T balance functions as a second line of defence since the t–g feedback of renal autoregulation of RBF/GFR is not perfect. Like t–g mechanism, the G–T balance is also an intrinsic phenomenon. In euvolemia, when there is an increased filtered load, the proximal tubule will compensate by increasing the sodium and solute reabsorption and more water reabsorption also follows. However, in hypovolemia, priority is given to conserving sodium. The excreted sodium is reduced and this is affected by a lower filtered load together with an increased nephron sodium reabsorption, including at the proximal tubule. The renal sympathetic nerve and activation of the renin–angiotensin–aldosterone system decrease the sodium urinary output. The intrinsic G–T balance is masked and overridden.[4]

13. Drinking a Large Solution of Isotonic Glucose does *Not* Produce an Osmotic Diuresis

Increased rate of urine volume output is called diuresis. There are two versions of diuresis, water and osmotic. Water diuresis is due to the lack of ADH (vasopressin) action. This can be due to deficiency of secretion of the hypothalamic-osmoreceptor/pituitary mechanism or a dysfunction in ADH receptor binding at the collecting ducts. The name diabetes insipidus is given reflecting the dilute "tasteless" high-volume urine.

Osmotic diuresis occurs in association with the glucosuria in diabetes mellitus. The unreabsorbed glucose at the proximal tubule interferes with the iso-osmotic reabsorption of water.

Drinking isotonic glucose in healthy persons will not lead to glucosuria as the renal plasma concentration threshold for glucose is not exceeded. Under insulin action, cellular uptake of glucose rapidly occurs and a hypotonic expansion of the ECF results. The body responds to the positive water balance by excreting the excess water when the ADH secretion is inhibited by the hypo-osmotic ECF.

14. Water does *Not* Follow Sodium at the Renal Collecting Ducts.

Students frequently say that when sodium is reabsorbed at the collecting ducts, water will follow. This might sound correct. And when viewed at the intestinal epithelial cells, this iso-osmotic reabsorption of water is an accurate picture of how water is transported at the epithelium. The water movement at the proximal convoluted tubule is also an iso-osmotic reabsorption of water that follows sodium reabsorption which then generates a local osmotic gradient.

However, water is not iso-osmotically reabsorbed at the collecting ducts. Water movement is, however, osmotically driven at the collecting ducts, when made permeable by ADH, by the surrounding hyperosmotic medullary interstitium that is established by the unique renal countercurrent phenomenon.[5]

Physiologic thinking will tell us that water retention that "follows" sodium reabsorption is indirect and not *in situ* at the collecting ducts. As more sodium is reabsorbed at the collecting ducts as occurs in negative sodium balance with any fluid loss, the sodium retention then leads to activation of the osmoregulation mechanism. Water is then reabsorbed more at the collecting ducts made permeable by the action of ADH released from the hypothalamus–posterior pituitary osmoreceptor/ADH response system.

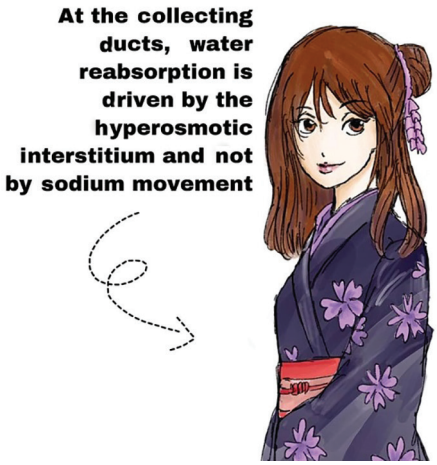

Fig. 5: Miss Take and hyperosmotic renal interstitium

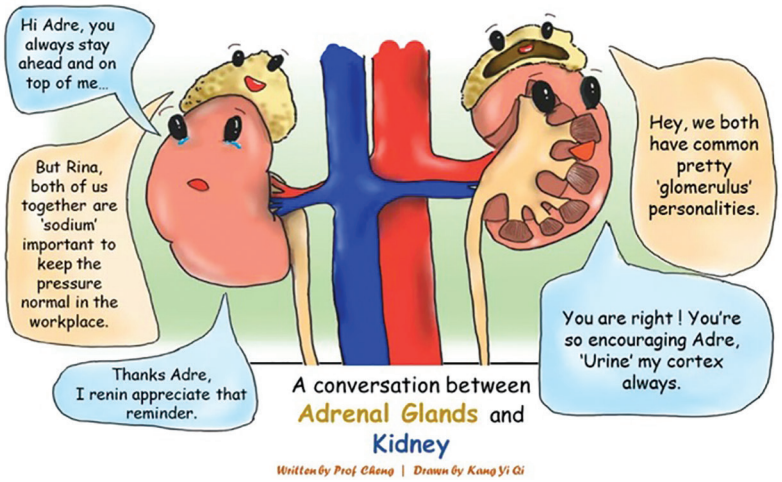

Fig. 6: A conversation between adrenal glands and kidney

ADH and aldosterone act on the same principal cells of the collecting ducts. And in the scenario of hypovolemia, both the levels of ADH and aldosterone are elevated in the blood. Thus the luminal permeabilities of the principal cells are increased at the same time to both water and sodium via stimulated number of aquaporins and sodium channels respectively. Water is reabsorbed, driven by the dominant hyperosmotic interstitium and sodium is reabsorbed and conserved also (Fig. 5).

15. I am (*Not*) Bringing my Books Back for the Holiday Break! A Humor to Engage the Students!

We recently created a Japanese character to enhance this NOTs physiology learning. Meet Miss Take, a female medical student. Miss Take is obviously a pun for "mistake." Miss Take is shown to make several negative statements, highlighting common misconceptions, to reinforce several definite mechanistic events in renal physiology. Arigato Miss Take! Credit to Sherly Lam Wai Ying my biomedical student for the art.

The adrenal glands, in particular the adrenal cortex has an integrated role with the kidneys in the homeostasis of ECF. The mineralocorticoid aldosterone is the key hormone in sodium balance regulation as well as in ECF potassium concentration control. Besides determining blood volume via the sodium homeostasis, the adrenal glucocorticoid cortisol is needed for optimal vascular responsiveness in blood pressure maintenance. Credit to Kang Yi Qi, a medical student from Universiti Sains Malaysia for the cartoon dialog between the Rina Kid and Adre (Fig. 6).

Conclusion

Our roles as physiology educators include stimulating thinking in Physiology, engaging the students with a quiver of arrows, questions that will direct them to focus and grasp essential concepts. Using these negative physiology statements and getting students to explain and untangle the NOTs are a useful approach to target inaccurate perceptions and strengthen the foundation in building and applying physiological knowledge.

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