Teaching the renal tubular reabsorption of glucose using two classic papers by Shannon et al.

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Braga VA. Teaching the renal tubular reabsorption of glucose using two classic papers by Shannon et al. Adv Physiol Educ 35: 114–116, 2011; doi:10.1152/advan.00108.2010.—Most of the transport along the nephron uses membrane proteins and exhibits the three characteristics of mediated transport: saturation, specificity, and competition. Glucose reabsorption in the nephron is an excellent example of the consequences of saturation. Two classic papers by James A. Shannon and colleagues clearly show the ability of the kidney in transporting glucose and its saturation process, providing students with examples of the handling of glucose by the kidney. In addition, these articles demonstrate how stable and reproducible is the transport maximum of glucose in the proximal tubule under different experimental conditions. One key figure from each classic paper can be used to give students insight into how glucose transport becomes saturated, resulting in the excretion of glucose in urine, and will also give students a clear example of how careful experimentation and a clear interest in renal physiology led Shannon and colleagues to advance the field.

Glucose transport; kidney; teaching points

Among the several important functions of the kidneys is their ability to maintain normal blood concentrations of solutes and water by balancing the intake of those substances with their excretion in urine, obeying the principle of mass balance. Most of this balance occurs along the nephron (the functional unit of the kidneys) by filtration, reabsorption, secretion, and excretion.

The most well-understood property of the nephron is its ability to transport substances by different mechanisms. Most transport in the nephron uses membrane proteins and exhibits the three characteristics of mediated transport: saturation, specificity, and competition.

Glucose reabsorption in the nephron is an excellent example of the consequences of saturation. At normal plasma concentrations, all glucose that enters the nephron is reabsorbed before it reaches the end of the proximal tubule. The tubule epithelium is well supplied with carriers to capture glucose as the filtrate flows past. If the blood glucose concentration becomes excessive, glucose will be filtered faster than the carriers can absorb it. The carriers will become saturated and unable to reabsorb all the glucose that flows to the tubule. The transport rate at saturation is called the transport maximum, known as $T_m$. As a result, some glucose escapes reabsorption and is excreted in the urine.

Among the several important physiologists throughout history that gave important contributions to the development of renal physiology as we know nowadays is Dr. James A. Shannon. Dr. Shannon is widely recognized in the scientific world for his contributions in kidney function, chemotherapy, and malaria (6–9). His career was devoted to medical research, teaching, and public health service. Born in 1904 in Hollis, NY, Dr. Shannon graduated from Holy Cross in 1925 and received his medical degree from New York University in 1929 and his PhD in Physiology from New York University in 1935. During World War II, Dr. Shannon played a prominent role in the malaria research activities of the National Research Council and acted as a consultant for the Secretary of War. In recognition of his work, he received the Medal of Merit, one of the highest awards for civilian service in government. In 1961, Dr. Shannon was also a recipient of the Mendel Medal award.

Regarding his numerous contributions to kidney function, we will focus on two of his papers, published in 1938 and 1941 in the American Journal of Physiology (6, 7), where he elegantly describes 1) the filtration, reabsorption, and excretion of glucose by the nephrons and 2) the stability and reproducibility of measuring glucose $T_m$ in dogs. The studies of Dr. Shannon and his collaborators are part of the American Physiological Society (APS) Legacy Project (http://www.the-aps.org/publications/legacy/).

Dr. Shannon formulated amazingly accurate predictions about the stability of the glucose transport system under different experimental conditions (6, 7). Like other great papers from the APS Legacy Project used for teaching physiology (1, 3, 11), these classic papers are particularly useful for teaching the principles of glucose transport by the nephron. Dr. Shannon’s paper published in 1941 (7) associated with his previous paper published earlier in 1938 (6) are really all you need to teach the fundamentals of glucose $T_m$ by the nephron!

The main findings of Dr. Shannon’s papers were as follows. First, the glucose reabsorptive system, as evaluated by glucose $T_m$, has considerable stability in normal dogs. Of note, there was no knowledge about Na+-glucose-linked transporter (SGLT) proteins at that time, which were described only 20 yr later. Second, the reproducibility of glucose $T_m$ measurements under different experimental conditions is excellent. Third, relatively few precautions need be observed in measuring glucose $T_m$ in the dog because of the stability that characterizes the system. Finally, any absolute concentration of glucose that results in frank diuresis will be adequate to saturate all the nephrons in the normal, well-hydrated dog, since further elevation does not result in any increase in glucose reabsorption.

In-Class Application

Students should have some introductory background in renal physiology and the glomerular filtration rate before this activity, either through assigned reading or through previous lectures and discussions. Among the assigned reading, it is mandatory that students have read both of Dr. Shannon’s papers (6, 7). For an in-class activity appropriate for undergraduates, both...
the articles and associated questions can be distributed to your students. For a 50- to 65-min in-class activity, the instructor may wish to introduce the historical context, general background, and experimental designs for Fig. 1 from Refs. 6 and 7 (presented here as Figs. 1 and 2) with a brief (20 min) lecture. Students can then work in groups of two to four students to answer the discovery learning questions for an additional 20–30 min. The groups can then reconvene for a 10- to 15-min class discussion of the data and questions.

Questions for Discovery Learning

Question 1. Draw a dashed line in Fig. 1 [extracted from the paper published in 1938 (6)] pointing out where the threshold for the appearance of glucose in urine is taking place.

Question 2. Using Fig. 1, explain why the excretion curve (curve B) parallels the filtration curve (curve A) after reaching a certain plasma glucose concentration.

Question 3. Describe the results of the following experimental groups. State them in “If . . . then” form. For example, “If normal dogs have water restriction, then their glucose excretion . . . ”
   A. Administration of adrenaline (intravenously).
   B. Administration of insulin (intravenously).
   C. Water restriction.

Question 4. What does glucose load/Tm = 2.0 mean?

Question 5. Suggest some clinical implications of these findings:
   A. What would happen to glucose Tm in diabetic patients fed a high-glucose diet?
   B. Would uninephrectomy affect glucose excretion in patients immediately after surgery?
   C. Will glucose Tm change in a patient with a pancreatic tumor making too much insulin?

Home Assignment

After the in-class activity regarding Dr. Shannon’s papers, students will have home assignments for the next class regarding what the current state of knowledge concerning SGLTs in the kidney. As students have learned, Shannon’s work helped to set the foundation; now students will be given a series of other papers related to what have we learned since Dr. Shannon’s discoveries. In addition to diabetes mellitus, other diseases of the SGLT family that can cause glucosuria will be explored. In addition, the development of selective SGLT-2 inhibitors to essentially reduce the Tm for glucose in the tubule, resulting in the loss of glucose in urine, will be discussed in the next in-class activity (suggested Refs. 2, 4, 5, and 10).

Teaching Points

Teaching point 1. The y-axis of Fig. 2 (Fig. 1 from Ref. 7) represents glucose reabsorption/Tm. The x-axis represents glucose load/Tm. It is clear that as the glucose load increases until a certain point, known as Tm, glucose reabsorption increases linearly. After Tm is reached, glucose reabsorption remains constant despite a further increase in the glucose load. The same conclusion can be achieved by analyzing Fig. 1 (Fig. 1A from Ref. 6), which might be even more student friendly. It is important to note that the Tm for dogs is slightly lower than that found in most physiology textbooks for human Tm, mainly due to differences between species. Students should be warned of that important point. In addition, the “threshold” values discussed in Dr. Shannon’s papers should not be confused with what is now called the renal plasma threshold (in mg/dl) in many textbooks.

Teaching point 2. Tm was strikingly constant and reproducible over time and among animals under different experimental conditions, such as the administration of insulin or adrenaline and a change the dietary protein content (Tables 1–3 from Ref. 7).

Like most good physiological studies, there were several elegant control procedures that were adopted and serve as excellent teaching points as well:

Teaching point 3. Plasma creatinine clearance was used to estimate the glomerular filtration rate.

Teaching point 4. Cyanol solution was intravenously injected to determine the renal dead space when a rapid change in the glucose plasma level took place.

Fig. 1. Original Fig. 1A from Shannon and Fisher in 1938 (6) showing glucose filtration, reabsorption, and excretion (in mg·min⁻¹·100 ml⁻¹ of glomerular filtrate). Curve A (solid circles) shows the rate of glucose excretion, curve B shows glucose filtered at various glucose concentrations, and curve C (open circles) shows the rate of glucose reabsorption.

Fig. 2. Original Fig. 1 from Shannon et al. in 1941 (7) showing the effect of rapid falling plasma glucose concentrations on renal tubular reabsorption. Each solid circle represents the ratio observed in a single experimental period. Tm, transport maximum.
Using Classic Papers to Teach Physiology

Teaching point 5. The animal was hydrated with water, considering that glucose acts as an osmotic diuretic in the proximal tubule.

In summary, Dr. Shannon’s papers have an enormous number of teaching points. Your students will not only learn the essence of the glucose handling by the nephron but will also gain an appreciation for the elegance of experimentation without the support of the technological arsenal available nowadays.

DISCLOSURES
No conflicts of interest, financial or otherwise, are declared by the author(s).

REFERENCES