ESSAYS ON APS CLASSIC PAPERS

Postnatal developmental renal physiology: a study of historic significance

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This essay looks at the historic significance of an APS classic paper (http://www.the-aps.org/publications/classics/) that is freely available online:


INFANTS DRINK MOTHER’S MILK, which is a hypotonic solution, and thus must be able to excrete a hypotonic urine from birth. In addition, under conditions of stress the neonate and infant must have some protection against volume depletion with conservation of salt and excretion of hypertonic urine. In Dr. Gertrude Falk’s classic paper entitled “Maturation of Renal Function in Infant Rats” published in 1955, she examined the maturation of renal function during postnatal development in rats (10). She examined several of the basic functions of the kidney in adult and neonatal rats and compared the glomerular filtration rate, rates of excretion of a water load and salt load, and the ability to concentrate urine when deprived of food and water for 24 h. This study set the standard for how to carefully characterize immature renal function and the response of the neonate to environmental stress.

Several of the observations in this manuscript had been demonstrated previously by others. Remarkably, many developmental studies performed at this time used normal human neonates and infants (8, 9, 16, 18). Neonates and infants have a lower glomerular filtration rate than adults even when corrected for body surface area (9, 18, 20). Neonates that are administered a water load have a delayed excretion of a comparable amount of water per body weight as adults (13, 16). This has significant importance to human neonates, who can develop hyponatremia and seizures when given formula diluted with too much water (7). Previous studies had examined the effect of water and food deprivation on the urinary concentrating ability of neonatal rats and demonstrated that the maximal concentrating ability is far less than that of the adult (12).

Dr. Falk (Fig. 1) went considerably beyond the previous descriptive studies comparing renal function in adults and neonates. In the introduction to her paper, she stated that “The aim was to determine quantitatively to what extent renal function was altered during the postnatal period and to correlate changes in response to different stimuli. Such a study of maturation offers the possibility of identification of factors involved, by comparison of stages within a species relatively immature at birth. Ontogenetic changes in the alimentary tract, kidney, circulation and endocrine organs have been considered.”

In her manuscript she performed an extensive examination to determine why neonatal rats have an impaired ability to excrete a water load administered into the stomach compared with adults. She ruled out a difference in the rate of gastrointestinal absorption in neonates and demonstrated that there was impaired renal excretion of water. Nephrogenesis continues in the rat until approximately day 10 of life so a lower glomerular filtration rate could be a factor impairing urinary excretion of a water load. To this end she examined the effect of a water load in neonatal uninephrectomized rats. She did not find a difference in the rate of renal excretion of a water load, and her approach was meticulous and experiments well designed. She concluded that the reduced glomerular filtration rate was not the primary effect limiting excretion of free water. Her paper went on to examine whether the reduced ability to excrete free water in neonates was due to factors present in the adrenal cortex and adrenal medulla. She found that administration of adrenal cortical extract or catecholamines caused an increase in the ability of neonates to excrete free water. The water load was administered at the same time as these hormones, so the increase in urine dilution was likely due to hemodynamic factors that increased glomerular filtration rate and NaCl delivery to the diluting segment. She also examined why neonates are not able to concentrate their urine to the same extent as adults. She found that neonates had an attenuated response to the action of vasopressin compared with adults. In addition, she showed that the pituitary gland of the neonate could respond to nicotine to cause an attenuation in water excretion comparable to that seen with exogenous administration of vasopressin.

Fig. 1. Gertrude Falk (photograph courtesy of Martin Rosenberg).
The approach used by Dr. Falk to determine the factors responsible for developmental changes in renal function set many of the guidelines used by developmental physiologists today. One must appreciate that the ability to measure many of the factors responsible for postnatal development were not possible at that time. In her study she carefully examined the ontogeny of changes in the ability of the neonatal kidney to concentrate and dilute urine. This approach was insightful and has subsequently been used by most investigators in developmental physiology since the maturational change in a physiological function usually correlates with a change in the expression of a factor or hormone that is involved in promoting the developmental change. This often gives the first clue to the factor(s) involved. If a factor is involved in a developmental change in renal function, then administration of the factor prior to the physiological increase would accelerate the maturational change. This was an approach outlined by Dr. Falk in experiments where she examined various hormones or glandular extracts could increase urinary concentration or dilution to levels seen in adults. Developmental physiologists also determine whether prevention of the maturational change in a factor thought to be responsible for a developmental change in function is abrogated if that factor is prevented from having a change in levels from that seen in the neonate. Her examination of the effect of neonatal nephrectomy on urinary dilution was clearly along this line of reasoning. Finally, developmental physiologists want to see whether the effect of a developmental factor can be demonstrated in vitro. Clearly, this was beyond the capabilities of the time.

Studies of postnatal renal development have led to several unexpected results. The neonatal kidney is not just a smaller version of an adult kidney with identical mechanisms of renal transport. Developmental studies found differences in water and electrolyte transport that could not be accounted for by transporters studied in adult animals. These findings include the recognition of a neonatal Na\(^+\)/H\(^+\) exchanger, NHE8, responsible for a significant fraction of proximal tubule acidification in the neonate but which is of yet unknown significance in the adult (3, 11). Developmental studies led to the discovery of a “neonatal” sodium-dependent phosphate cotransporter in rodents that ironically is the predominant sodium-dependent phosphate cotransporter in the adult human kidney (4, 14, 15, 19). There have been developmental changes not only in transcellular transport but also paracellular transport that were found to be due to the expression of claudin isoforms present in neonatal but not in adult kidney (1, 2). The impaired ability to concentrate urine in the neonate to the same extent as adults turned out to be quite complex and due to a number of factors (5). This was in part due to developmental changes in signal transduction in response to vasopressin in the collecting duct (6, 17). The insight into what induces developmental changes in kidney function has come forth using the same approach outlined in the studies in this classic paper.

Professor Falk spent most of her scientific career at the University College London in the Department of Biophysics and Physiology, where she was the first woman to become a professor. Her work at the University College London focused on the study of photoreceptor cells in the retina, and she pioneered the use intracellular microelectrodes to study phototransduction. Professor Falk played an active role in politics. She was a member of Jews for Justice for Palestinians and campaigned for a fair negotiated settlement in the Arab-Israeli conflict. In her later life she protested against closure of medical services for the mentally impaired and the elderly. She is remembered by her colleagues for her warmth, encyclopedic memory, sense of humor, and her great sense of fair play. Professor Falk passed away last year at the age of 82. Her scientific career spanned 50 years.

REFERENCES