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COMPARATIVE ASPECTS OF RENAL FUNCTION

Evolutionary aspects of renal function

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Evolutionary aspects of renal function. In his hypothesis of the evolution of renal functions Homer Smith proposed that the formation of glomerular nephron and body armor had been adequate for the appearance of primitive vertebrates in fresh water and that the adaptation of homoiotherms to terrestrial life was accompanied by the appearance of the loop of Henle. In the current paper, the increase in the arterial blood supply and glomerular filtration rate and the sharp elevation of the proximal reabsorption are viewed as important mechanisms in the evolution of the kidney. The presence of glomeruli in myxines and of nephron loops in lampreys suggests that fresh water animals used the preformed glomerular apparatus of early vertebrates, while mechanisms of urinary concentration was associated with the subdivision of the kidney into the renal cortex and medulla. The principles of evolution of renal functions can be observed at several levels of organizations in the kidney.

In celebrating the 100th anniversary of Homer W. Smith's birthday, it is appropriate to recall the avenues modern renal physiology have taken since his seminal studies. As so often found in science, what is eventually found is seldom expected. Still, the most important measure of Smith's science is the significance of the studies initiated by his pioneering investigations. The fundamental theme in Smith's creativity is evolution in general and the evolution of renal functions in particular. More than six decades have passed since the beginning of Smith's work, and five decades have passed since the time of the Porter Lecture, "The evolution of the kidney" [1]. Generations of physiologists have now been reading *From Fish to Philosopher* with great interest for more than four decades [2]. This symposium has been organized under the auspices of the Mount Desert Island Biological Laboratory to which Smith has contributed greatly. It is also in this Laboratory where many fundamental studies in comparative renal physiology have been carried out. On one of the laboratory buildings a bronze plaque reads: "Dedicated to Honor His Pioneering Contributions to Renal and Comparative Physiology and the Philosophy of Science."

In this paper, new aspects of the evolution of renal function are considered. These aspects had not been formulated in the fifties, and since then have been derived from the advantages afforded by physiology and related disciplines. Addressing some of the important questions in the evolution of renal physiology I will consider here: stages in the evolution of renal structure and function from primitive sea agnatha to mammals and principles of evolution of renal function.

Methods of evolutionary physiology of the kidney

The domain and range of comparative and evolutionary renal physiology differ significantly and offer a variety of methodological approaches to the study of the pathways taken by evolution. Data of comparative physiology alone are insufficient in view of some limitations imposed by peculiarities in the particular animal species of interest. To reconstruct stages in the morphological-functional evolution of the kidney, two principal methods are used: those of comparative physiology that focus on phylogenetic changes and improvements of function, and those ontogenetic methods that focus on the development of functions during embryogenesis and the postnatal period. Clinical material is also of interest because dysfunction during disease often resemble earlier stages in evolution [3]. Furthermore, the study of animal adaptation to various conditions in the external environment, potentially damaging and life-threatening situations, and unique stressful conditions of special environments, gives insights into functional reserves and evolutionary plasticity. Paleontologic data are essential for reconstructing the picture of evolution, and definite conclusions can be made based on studies of paleophysiology and paleobiochemistry. Of interest are also studies in pharmacology and toxicology because sensitivities to physiologically active substances in lower vertebrates and immature, postnatal animals often differ from those in respectively higher vertebrates and adult animals.

Principles of evolution of renal functions

Smith [2] believed that the unique functional feature of the mammalian kidney—its power of urinary concentration—is accompanied by only two notable anatomical changes: the appearance of the loop of Henle, and the disappearance of the renal-portal system. His ideas stimulated others to ponder questions about the evolution of renal functions. Schmidt-Nielsen mused, "*It was characteristic of Smith that he [Smith] oversimplified the explanations of physiological phenomena. But I consider this an important trait, which had the effect of stimulating other people to think, experiment, and challenge his postulates*" [4].

To characterize the evolution of function, two approaches may be used. The first consists of tracing a particular function from lower to higher forms of life. The second considers any given stage of development of physiology to reflect the main features of renal functions.

In modern physiology, including evolutionary physiology [5], increasing attention has been paid to the study of molecular mechanisms. At the same time, there are increasing calls to interpret the significance of molecular processes for the whole organism. The term "function" has now much broader meaning than the specific activity of a particular organ, even if it is the primary organ of that function. For example, the maintenance of interior milieu requires a number of organs and systems, although the kidney is the main effector organ in higher vertebrates [2, 6, 7].

Evolutionary morphologists have made great contributions to the principles of evolution in organ function. To characterize the state and evolution of any one function, it is necessary to consider the evolution of the organ system at every major level of organization: (1.) the highest level of organization, that is, the functional system of, for example, water and electrolyte homeostasis; (2.) one of the organs of homeostasis, the kidney; (3.) the morphological unit of the kidney, the nephron; and (4.) the specialized cells of the nephron, renal epithelial cells. The principles of evolution are described below for each of the above-mentioned levels.

Evolution of kidney function

Acquisition of multiple functions

The idea of the kidney as merely an organ of excretion by no means reflects the many homeostatic functions it performs [2, 7]. In the course of evolution the number of renal functions has increased. In myxines, the kidney alone is not capable of providing osmoregulation as, for example, the excretion of a hypotonic urine; in lampreys and fresh-water fish, the kidneys are capable of excreting a dilute urine [8, 9]. Renal osmoregulatory functions develop gradually in postnatal ontogensis of mammals [10]. Mechanisms of water conservation via arginine-vasotocin (AVT) are first formed in anurans, while the kidneys of homoiotherm vertebrates are the first to maintain water and electrolyte balance through the development of urinary concentrating ability under conditions of extreme water deficits [11–13]. Kidneys in vertebrates, particularly those in mammals, perform many additional functions. They take part in the regulation of extracellular fluid volume, the concentration of osmotically active substances, the regulation of plasma pH, the excretion of unwanted products of metabolism, the metabolism of proteins, carbohydrates and lipids, and the catabolism of peptide hormones. In addition, they produce physiologically active substances regulating blood pressure, blood coagulation, and Ca^{2+} balance as well as substances that modulate the effects of hormones.

Intensification of organ function

The mass of the vertebrate kidney (in mg/100 g body wt) is rather constant in heterothermic and homeothermic animals of similar weight: 553 ± 4.9 in lampreys, 382 ± 9.7 in frog, 523 ± 31 in pigeon, and 669 ± 15 in rat (SE, $N = 10$). Yet the glomerular filtration rate (and therefore rates of tubular reabsorption) increase sharply in homoiotherms [8]. In cyclostomata and fish glomerular filtration rates are 20 to 100 (and even 1000) times lower than those in mammals. The same is true to tubular reabsorption rates of ions [8, 14]. This sharp increase in the intensity of solute transport in the kidney creates beneficial effects by increasing the precision of fluid, electrolyte, and nonelelctrolyte balance. At the same time the rapid renal turnover requires a drastic rise in the energy expenditure of the kidney. The highest level of blood perfusion is achieved in the mammalian kidney. At rest, up to 20% of the cardiac output flows to the kidney, and renal oxygen consumption is nearly 10% of whole body oxygen consumption. This intensification of renal work reflects the evolution of the kidney rather than a consequence of homoiothermity, because in warm-blooded mammals the rates of glomerular filtration and tubular transport also increase after birth [10].

The need to eliminate from the body substances such as divalent ions in marine fish, uric acid in reptiles and birds with low rates of glomerular filtration is met by another variant of renal circulation [15]. Except for cyclostomes, fresh water fish and mammals, most vertebrates possess a renoportal system that perfuses the kidney with venous blood from caudal regions of the animal. This venous perfusion markedly increases the potential for excretion via tubular secretion [8]. Hence, the primacy of arterial blood supply and the intensity of reabsorptive tubular transport and metabolism in mammalian kidneys are features characteristic of warm-blooded vertebrates.

Modification of organ structure

The evolution of urinary concentration finds its highest development in mammals. Urinary concentrating ability appears concomitantly not only with the elongation of the thin segment, as discussed by Smith [2], but also with the subdivision of the kidney into a cortex and medulla. Previously it was considered that urinary concentrating ability was related to the appearance of the loop of Henle. However, structurally similar loops of the nephron have been discovered in the lampey kidney [8]. Most likely, the subdivision of the kidney into cortical and medullary regions, a high level of arterial blood supply, and the elaboration of tubular loops combine to endow mammalian and avian kidneys with the ability to form a concentrated urine. Urinary concentating ability is also gradually formed in the ontogenesis of mammals [10], and is first to be injured in renal pathologies. Urinary concentrating ability also changes under experimental conditions, particularly after space flight [8].

Oligomerization of organs and polymerization of functional units

The decrease in the number of organs is characteristic for the evolution of multicellular organisms. Metamerically located nephridia are replaced by paired excretory organs in molluscs (Bonjanus' organ), arthropods (antennal or maxillary glands), and vertebrates (paired kidneys). In parallel, the number of renal functional units, the nephrons, increases. For example, the number of nephrons per 1 g of renal mass varies widely: 7,600 in the frog *Rana temporaria* and 73,680 in the sand rat *Psammomys obesus* [15].

Switching organs or functions within the organ

Adaptation to new environmental conditions can bring about a change in organ function and/or a switch to other organs. Adaptation of fish to life in the sea is made possible through the participation of a number of organs of osmotic regulation. Marine animals drink sea water and desalinate it via the secretion of sodium and chloride across the gill (fish) or salt glands (reptiles and birds) [14]. Thus, adaptation to the hyperosmotic environment of the sea was possible through major involvements of gill and nasal salt glands in osmotic and ionic regulation. It is only in mammals that this regulation is primarilty performed by the kidney.

Regress of functions

In marine teleosts the number of glomeruli is reduced and some species have entirely discarded the renal distal tubule [2, 11]. In parallel, the ability to secrete magnesium, sulfate and other divalent ions was developed. These changes in renal cell activity seem to be based on the presence of primoidal tubular transport systems, secretion of magnesium and calcium via Na^+/Mg^{2+} and Na^+/Ca^{2+} exchange transport, respectively [8, 16].

Evolution of nephron function

The heterogenous populations of nephrons contribute to urinary concentration in different ways [7]. Mammalian nephrons with a long loops of Henle facilitate the accumulation of sodium and urea in the medullary interstitium, and short loops of Henle in birds and mammals facilitate the accumulation of only sodium and chloride [12]. Together they generate an increasingly hyperosmotic renal interstitium with depth into the renal medulla.

Increase in differentiation

Glomeruli, proximal and distal segments are present in the kidneys of nearly all vertebrates, from cyclostomata (lamprey) to mammals. The increase in the differentiation of the distal tubule is clearly seen in homoiotherms [15]. This differentiation involves epithelial cells of the nephron as well as cell junctions between them [8]. Accordingly, the differentiation of cells and their junctions provide for a leaky epithelium with high transport rates at the proximal segment of the nephron and a tight epithelium with low transport rates at the distal segment of the nephron.

Increase in the intensity of reabsorption and secretion

In mammalian proximal tubules, rates of fluid reabsorption per unit of tubule length are higher than in proximal tubules of poikilotherm vertebrates. Rates of fluid reabsorption also rise during the ontogeny of mammals [8, 17]. In cases where it is necessary to excrete particular kinds of solutes (Mg^{2+}, $SO_4{}^{2-}$ in marine teleosts), a molecular mechanism is formed for the rapid secretion of these solutes.

Formation of morphofunctional complexes

The activity of nephrons is closely connected with the renal vascular system. Of great importance is the renal interstitium. In homoiotherms, the capacity to form a concentrated urine rests largely on the presence of a hyperosmotic renal interstitium formed by the activities of the loop of Henle, the vasa recta, and the collecting duct [7, 15].

Increased opportunities for regulation of functional activity

The increase in the differentiation of nephrons provides for increased opportunities for adaptations of renal functions. For example, the failure to reabsorb solute or water in proximal parts of the nephron may be corrected in more distal parts. In mammals, a decrease in maximal reabsorption rates of NaCl by proximal tubules can be accompanied by a compensatory increase of reabsorption in the thick ascending limbs of the loop of Henle. Thus it appears that the rise in glomerular filtration rate and tubular reabsorption paralleled the evolution of the thick ascending limb and the distal tubules to develop a powerful system for the reabsorption of a number of ions. This system has a wide functional range to address qualitative and quantitative challenges presented to it from more proximal regions of the nephron.

Evolution in functions of specialized cells

Formation of asymmetrical cell

In the evolution of nephron epithelial cells, specializations of apical and basolateral membranes provide the opportunity for vectorial transport [7, 8]. The strategic location of channels, pumps and carriers at these two membranes provides for tubular reabsorption in one case and tubular secretion in the other. Molecular transport mechanisms can nearly disappear from one membrane and appear in the other, providing mechanisms for switching the direction of transepithelial transport.

Formation of specialized ultrastructures

Qualitative and quantitative differences in the characteristic apical and basal membranes of the tubular cells from the basis for transepithelial transport in reabsorptive and secretory directions. The molecular properties of the apical cell membrane differ along the length of the nephron: apical membranes of the proximal tubule reabsorb fluid, electrolytes, glucose, amino acids and proteins from the tubular fluid to return them to the blood. In cells of the proximal tubule numerous pinocytosis vesicles are responsible for the reabsorption of proteins and their subsequent hydrolysis for reabsorption. In other tubule segments the molecular mechanisms of organic solute transport is absent since only ions are reabsorbed here.

During the evolution of the kidney, the intensity of reabsorption and secretion of substances increases in the proximal tubules [8, 18]. Since renal weight normalized to the size of the animal does not change, and since the relative length of the proximal tubule remains constant, the intensification of transport must require the intensification of work by the tubule cells. This is confirmed by the large number of mitochondria, the increased number of mitochondrial cristae, the activation of enzymes of the energy metabolism, and the increase in the number of folds in the basolateral membrane, that provide increased surface areas for the localization of Na^+,K^+-ATPase [8].

The evolution of nephron cells is related to specializations of cell junction. In mammalian renal proximal tubules the tight junction is highly permeable to monovalent ions but impermeable to numerous nonelectrolytes; its electrical resistance is approximately $5\ \Omega \cdot cm^2$. In the most distal mammalian nephron and collecting tubules, electrical resistance reaches several thousand $\Omega \cdot cm^2$. The tubule wall is poorly permeable to ions and nonelectrolytes, and the ultrastructure of the tight junction is different from that in the proximal tubule. Amphibian proximal tubules are less permeable to ions than mammalian proximal tubules. Here the electrical resistance reaches $50\ \Omega \cdot cm^2$ [8].

There are also changes in the character of regulatory effects such as the effects of arginine-vasotocin (AVT) on water permeability in amphibian tubules [19], and the response of calcium-reabsorbing systems to parathormone [19, 20]. Responses to toxic substances also change. Injection of cisplatin, an antitumor drug, results in injury of the proximal tubule cells and nephrotoxicity in homoiotherms, whereas the same dose of this drug has no toxic effects in poikilotherms nor during early mammalian ontogenesis.

Concluding remarks

In this paper only a small part of problems dealing with evolution of function has been considered. Diversity of form of the functional organization of excretory organs in vertebrates and invertebrates is characterized by a common plan of their structure and activity [21, 22]. Almost without discussion remain the molecular and membrane basis of the evolution of function. The considered principles of the evolution of function were not related to advances in the theory of evolution. This article has concentrated only on characteristics of the main principles of the evolution of function at several levels of kidney organization.

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