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Renal reabsorption of phosphate during development: tubular events*

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Abstract. Studies performed in our laboratory on the isolated perfused kidney of the guinea pig have demonstrated that the rate of Pi reabsorption is substantially greater in the newborn than in the adult, when appropriate corrections are being made either for differences in glomerular filtration rate (GFR) or in renal tubular mass. In order to determine the location of this enhanced reabsorption along the nephron, micropuncture experiments were performed on euvolemic, non-fasted guinea pigs 5–14 and 42–49 days of age, maintained on standard guinea-pig chow diet (0.76% Pi). Concomitant measurements of overall kidney function were also obtained. The results confirmed that fractional reabsorption of Pi (TRPi%) across the entire kidney was significantly higher ($P < 0.01$) in the newborn ($89.93 \pm 2.55\%$) than in the adult ($78.25 \pm 2.89\%$) animals. The difference was also significant ($P < 0.05$) when TRPi was expressed in mol/ml GFR (1.87 ± 0.14 vs 1.53 ± 0.12, respectively). At comparable locations along the proximal tubule (TF/P_{in} of 1.90 ± 0.16 in the newborn, and 1.79 ± 0.15 in the adult, $P > 0.70$), the fraction of the filtered load of Pi reabsorbed was significantly higher ($P < 0.001$) in the immature ($76.66 \pm 2.74\%$) than in the mature ($67.21 \pm 2.74\%$) guinea pigs. Estimates based on the differences between proximal Pi reabsorption and the urinary excretion of Pi indicate that the reabsorption of Pi in tubular segments located beyond the proximal tubule is also enhanced in the newborn when compared with the adult ($15.62 \pm 2.11\%$ vs $10.51 \pm 1.83\%$, respectively, $P < 0.05$). Alternatively, this finding may be interpreted to represent a higher fractional reabsorption of Pi by deep nephrons.

Key words: Phosphate – Proximal tubule – Development – Guinea pig

Introduction

The maintenance of a positive external balance for inorganic phosphate (Pi) is required for the growth of newborn animals and humans. The contribution of the kidney to the conservation of Pi and the mechanism responsible for it are matters of past [1, 2] and current interest. Clearance studies performed in infants and children suggested that the low glomerular filtration rate (GFR) prevailing at an early age plays an important [3], if not exclusive [4] role in the retention of Pi. On the other hand, clearance studies performed in animals, in which care has been taken to control the factors known to affect renal Pi transport, have provided evidence that higher rates of tubular reabsorption, rather than lower filtration rates, account for the retention of a higher fraction of the filtered load of Pi by the kidney of the growing subject [5, 6]. Experiments with isolated perfused kidney preparations done in our laboratories [7] have demonstrated that the rate of renal Pi reabsorption is significantly greater in the newborn than in the adult, after corrections for differences in GFR or renal tubular mass are made.

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These high rates of Pi reabsorption are surprising in view of the morphological immaturity of the S1 segment of the proximal tubules [8, 9], the site where most of the Pi is reabsorbed in the adult [10, 11]. Furthermore, the low levels of Na^+-K^+-ATPase activity in the proximal tubules of immature rats [12] and rabbits [13] suggest a degree of functional immaturity expected to affect the Na^+-Pi cotransporter. By comparison, the distal segments are at a more advanced stage of development. Studies of sodium handling in young animals performed in this and other laboratories have demonstrated that the distal segments of the nephron [14, 15] possess a high reabsorptive capacity that contributes to the net positive Na^+ balance observed during postnatal development [16]. In addition, since during the newborn period PTH levels are low [17, 18] and the kidney appears to be resistent to the phosphaturic effect of this hormone [19, 20], the distal tubule may be further stimulated to reabsorb larger amounts of Pi. Indeed, a large capacity for Pi reabsorption distal to the proximal tubule has been demonstrated in adult thyroparathyroidectomized dogs which were volume expanded with saline [21], as well as in other experimental models characterized by the inhibition of proximal reabsorption [22]. It was, therefore, logical to postulate that in the newborn, the distal segments of the nephron compensate for the marked immaturity of the proximal convoluted tubule, resulting in the reabsorption of Pi in amounts sufficient to assure the positive external balance that characterizes a growing organism. The purpose of the present study was to identify the nephron sites responsible for the enhanced Pi reabsorption known to occur in the guinea pig during development, and to quantify the contribution of each of these segments to the overall renal reabsorption of Pi.

Materials and methods

In vivo micropuncture experiments were performed in guinea pigs of either 5–14 days (newborns) or 6–8 weeks (adults) of age. The newborns were weaned on day 2–3 of life and a standard guinea-pig diet containing 0.76% Pi was provided ad libitum up to the time of experimentation. Anesthesia was achieved by intraperitoneal injection of thiobutabarbital (Inactin) 90–110 mg/kg body wt. and the animals were prepared for micropuncture as previously described [23]. Polyethylene catheters (PE 50) were placed in the right jugular vein for infusion of solutions and in the right carotid artery for blood sampling and pressure monitoring. The ureters were catheterized (PE 10 or PE 50) and the urine was collected under oil in weighed containers.

The euvolemic state was maintained by continuous infusion of a solution containing equal volumes of isoncotic littermate plasma and 5% dextrose in 0.33% NaCl at a rate of 0.02 ml/min per 100 g body wt. Upon completion of surgery, the rate was lowered to 0.01 ml per 100 g body wt. and a priming dose of 5% inulin in saline was given (0.05 ml/100 g body wt.) followed by a constant infusion at a rate of 0.01 ml/min per 100 g body wt. Following 46–60 min of equilibration, a 40 µl blood sample was obtained and two 30-min urine collection periods initiated. Between 2 and 4 superficial proximal tubules were punctured in each animal with sharpened 6 µm tipped glass pipettes and 2- to 3-min collections of tubular fluid were obtained. The punctures were performed either at random or towards the end of the proximal convoluted tubules, identified by the injection in the jugular vein of a 0.05 ml bolus of a 0.5% sol. of lissamine green. A second sample of blood was taken upon completion of the clearance period and the urine volume measured. The blood samples were centrifuged, hematocrits were measured and aliquots removed for inulin determination. Measurements of Pi concentration in plasma and urine were made by the method of Fiske and Subarow [24]. Tubular fluid volumes were measured in a constant bore capillary and aliquots of 1–2 nl were transferred into 10 to 12 µm tipped pipettes approximately half filled with hydrated mineral oil. About 10–12 nl mineral oil was drawn into the tip in order to secure the sample and to avoid loss due to evaporation. Samples were carefully labelled and kept frozen until subjected to electron probe microanalysis [25]. (The sample preparations for electron probe were performed at the National Biotechnology Resource in Electron Probe Microanalysis, Harvard Medical School, Boston, Mass., USA.) Aliquots of 3–5 nl volume from the remaining tubular fluids were drawn in quartz pipettes and inulin was measured by the method of Vurek and Pegram [26]. Plasma and urine were always analyzed simultaneously.

Differences between the two age groups were determined by *t*-test statistics for two means. Included in the analysis were only experiments in which all variables were measured concomitantly. Fractional reabsorption of Pi along the proximal tubule (FR_{Pi} prox) was calculated by the formula $1-(TF/P_{Pi} \times P/TF_{in})$. The fractional reabsorption along the distal nephron (FR_{Pi} dist) was calculated from the differences between the fraction of Pi remaining at the site of the proximal tubular sampling and that found in the final urine.

Results

Whole animal data (Table 1)

As expected, GFR increased by two-fold between the first (0.28 ± 0.06 ml/min per g KW) and the seventh (0.55 ± 0.00 ml/min per g KW) week of postnatal life ($P < 0.01$). Fractional excretion of sodium (FeNa %) was somewhat higher in the mature (0.59 ± 0.14) than in the immature (0.24 ± 0.09) animals, but the difference did not reach statistical significance ($P < 0.1$). The serum Pi concentration was similar ($P > 0.90$) in the two age groups (2.18 ± 0.15 vs 2.16 ± 0.14 mM, respectively). The fractional reabsorption of Pi (TRPi %) was substantially higher ($P < 0.01$) in the newborn ($89.93 \pm 2.55\%$) than in the adult ($78.25 \pm 2.89\%$) guinea pigs. Similarly, the TRPi (µmol/ml of GFR) was 1.87 ± 0.14 in the newborn and 1.53 ± 0.12 in the adult ($P < 0.05$).

Table 1. Whole animal data

	GFR (ml/g KW)	FeNa (%)	Plasma Pi (mM)	TRPi	
				(% filtered load)	(μmol/ml GFR)
Newborn ($n = 8$)	0.28 ± 0.06[a]	0.24 ± 0.09	2.18 ± 0.15	89.93 ± 2.55	1.87 ± 0.14
Adult ($n = 9$)	0.55 ± 0.05	0.59 ± 0.14	2.16 ± 0.14	78.25 ± 2.89	1.53 ± 0.12
P	< 0.01	< 0.1	> 0.9	< 0.01	< 0.05

GFR = glomerular filtration rate; TRPi = fractional reabsorption of phosphate
[a] Mean ± SEM

Table 2. Single nephron data

	SNGFR nl/min	TF/P_{in}[b]	TF/P_{Pi}[b]	FR_{Pi}(prox)[b] % filtered load	FR_{Pi}(dist)[c] % filtered load
Newborn ($n = 8$)	5.05 ± 0.49[a]	1.90 ± 0.16	0.50 ± 0.11	76.66 ± 2.75	15.62 ± 2.11
Adult ($n = 9$)	18.68 ± 0.82	1.79 ± 0.15	0.54 ± 0.04	67.21 ± 2.74	10.51 ± 1.83
P	< 0.001	> 0.7	> 0.6	< 0.001	< 0.005

[a] Mean ± SEM
[b] Late proximal convoluted tubule
[c] Renal tubule beyond the proximal puncture site

Micropuncture data (Table 2)

The single nephron GFR increased from 5.5 ± 0.49 nl/min, during the first week of age to 18.68 ± 0.82 nl/min ($P < 0.001$), by the seventh week. The site of puncture along the superficial proximal convoluted tubule was similar in the two age groups, as reflected in the near identity of the TF/P_{in} ratios (1.90 ± 0.16 vs 1.79 ± 0.15, $P > 0.70$). Fractional reabsorption of Pi (TRPi %) plateaued in all animals at a TF/P_{in} of 1.5–2.0 (Fig. 1). However, the level reached was higher in the newborns than in the adults, reflecting a more complete reabsorption of the filtered load of Pi by the proximal convoluted tubule of the younger than of the older animals. Indeed, the proximal tubule reabsorbed 76.66 ± 2.75% of the filtered load in the newborn and 67.21 ± 2.74% in the adult ($P < 0.001$). An enhanced reabsorption of Pi may be also present in the distal segments of the newborn nephron. The fractional reabsorption of Pi distal to the proximal puncture site was 15.62 ± 2.11% in the newborns and 10.51 ± 1.83% in the adults ($P < 0.05$).

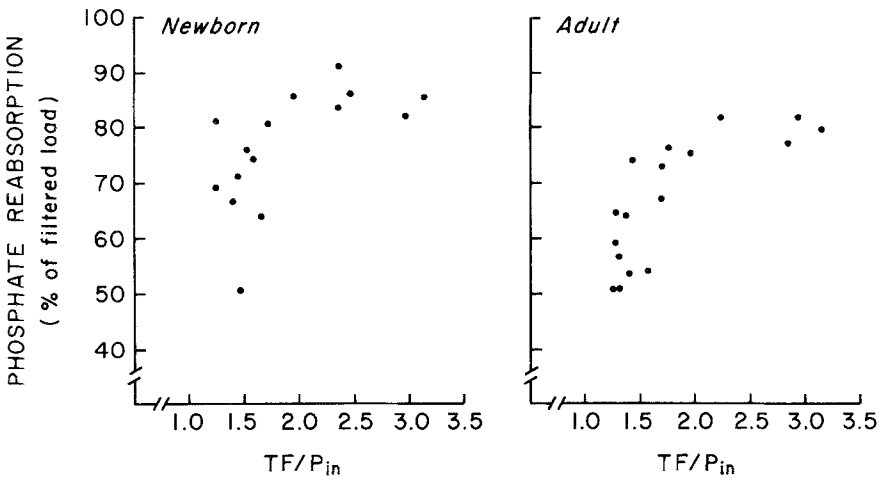

Fig. 1. Fractional reabsorption of phosphate (% of filtered load) along the proximal convoluted tubules of 5- to 14-day-old (newborns) and 42- to 49-day-old (adult) guinea pigs. Notice the higher levels of fractional reabsorption achieved by the newborn animals. The difference between the two age groups is statistically significant ($P < 0.05$)

Discussion

Concordant with previous results obtained by others in intact dogs [7] and rats [6] and with those obtained by us in the isolated perfused kidney of the guinea pig [5], newborns reabsorb proportionately more Pi than adults. In the current study, this is reflected in a higher TRPi/GFR ratio in the former than in the latter age group. It should be pointed out that these values do not represent maximal rates of transport, since the animals were not loaded with phosphate. Under these circumstances the true difference in reabsorptive capacity between the two age groups is not fully expressed. This is due to the fact that the TmPi is several-fold larger than the normal filtered load of Pi in the newborn, whereas in the adult it is only slightly higher than the filtered load observed under physiologic conditions [5]. This provides the newborn with a reserve which permits him to maintain a nearly complete renal reabsorption of Pi when the filtered load of Pi rises.

The role, if any, played by the low GFR in the enhanced reabsorption of Pi observed at an early age cannot be ascertained from these studies. Suffice to say that the GFR is low only when corrected for body or for kidney size, but not when corrected for proximal tubular size. The importance of this distinction will become apparent from this discussion.

Numerous investigators have demonstrated that the major renal site of Pi reabsorption is the early proximal convoluted tubule [27]. By various methods, such as free-flow micropuncture [28], microinjections [29] and the standing droplet technique [10, 11], the earliest part of the proximal tubule has been identified as having a greater capacity to reabsorb Pi than later segments of the nephron. Similar results have been obtained with isolated perfused tubule segments from rabbits [30]. Measurements performed in adult rats [31] have demonstrated that about 60% of the filtered Pi is reabsorbed by the point where the TF/P_{in} reaches ~2.0. At this location along the proximal convoluted tubule, the concentration of Pi has fallen to about 30% of the plasma concentration and then it remains relatively constant, indicating that the reabsorption of Pi along the remainder of the proximal convoluted tubule proceeds isotonically. Our findings illustrate that a similar pattern is obtained in the mature as well as in the immature guinea pig. At a TF/P_{in} of >1.5, peak levels of reabsorption have been reached at both ages. However, the percentage of the filtered load reabsorbed was significantly higher ($P < 0.001$) in the newborn than in the adult. Beyond this point along the proximal convoluted tubule, the fractional reabsorption of Pi remained stable (Fig. 1) both in the newborn and in the adult.

The fact that the newborn is able to reabsorb a larger percentage of the filtered load of Pi in the early portion of the proximal convoluted tubule is astounding in view of the structural and functional immaturity of this nephron segment. Evan et al. [8] have reported that the tubules located in the outer cortex of the 1-week-old rabbit consist of simple cuboidal cells with limited apical and basolateral membranes and lack of any segmentation. Even the proximal tubules of the inner cortex, which were at a more advanced stage of development and showed segmentation, were still quite immature compared with tubules obtained from adult animals. From a morphologic standpoint it took 25–30 days for the tubules of the inner cortex and 48 days for those in the outer cortex to reach maturity. During this period of time, the length of the juxtamedullary proximal convoluted tubule increased from 1.8 to 9.1 mm. More pertinent to the transport of Pi is the fact that most of the increase was due to lengthening of the S1 segment. Based on this study it can be estimated that the surface area of the luminal membrane increased by at least 600-fold in the S1 segments of the superficial proximal tubules and by about 60-fold in the juxtamedullary nephrons of the rabbit. Although such detailed information regarding the structural maturation of the guinea pig nephron is not available, observations made in other animal species such as the dog [9], the rat [32] and the pig [33] indicate that the same sequence of events applies. Moreover, micropuncture studies performed by us in guinea pigs [23] have demonstrated that the centrifugal pattern of change that characterizes the development of the kidney in animal species which have not completed nephrogenesis during intrauterine life, such as the rabbit and rat, can also be observed in animals born with a full complement of nephrons, such as the guinea pig. These morphological differences make it inappropriate to use tubular length as a correction factor when comparing the fractional reabsorption of Pi in newborn and adult animals. It is more reasonable to use the fractional reabsorption of sodium and water, which represents one and the same thing at all ages and has been shown to relate functionally to the fractional reabsorption of Pi.

By comparison with the proximal tubule, the distal tubular segments are better developed at this early stage of postnatal life [34]. This led us to

speculate that the ability of the immature kidney to reabsorb sufficient amounts of Pi is made possible by a high rate of reabsorption in distal nephron segments. Pertinent in this regard is our work on sodium homeostasis, which revealed the important role played by distal tubular reabsorption in the maintenance of the positive sodium balance prevailing during maturation [15]. Our finding that the newborn has a higher fractional reabsorption of Pi distal to the proximal puncture site than the adult may be the expression of a similar phenomenon. Likewise, the difference we observed may be due to the higher reabsorptive capacity of the deep nephrons. Indeed, in addition to axial heterogeneity, there appears to be differences in the capacity to reabsorb Pi between superficial and juxtamedullary nephrons, with the latter demonstrating higher reabsorptive rates of Pi than the former [35, 36]. Evidence in support of such heterogeneity has been provided by micropuncture studies in which collections of tubular fluid from the loop of Henle have allowed a comparison between the fractional reabsorption of Pi in deep nephrons with that of superficial nephrons [37]. The segment of the renal tubule where the increased fractional reabsorption of Pi occurs in the juxtamedullary nephrons is yet to be established. A discrepancy exists between results of micropuncture experiments, which indicate a proximal location [38], and measurements performed in isolated perfused tubules, which failed to demonstrate a difference in reabsorptive capacity between superficial and juxtamedullary proximal tubule segments [39].

A more detailed analysis of the role played by the various nephron populations in the overall reabsorption of Pi during development requires similar measurements. Unfortunately, the guinea pig is not an appropriate model for such experiments because of a lack of distal convoluted tubules on the kidney surface, while the rat and the rabbit undergo nephrogenesis for about 2 weeks after birth and therefore cannot be used for micropuncture studies in the immediate post-natal period. Whatever the ultimate outcome of such measurements might be, the current study demonstrates conclusively that the main contributor to the maintenance of the positive Pi balance intrinsic to the process of growth [40] is the proximal convoluted tubule. Description of the cellular mechanism by which this feat is accomplished is of great interest in view of the morphological and functional immaturity that characterize this nephron segment in the newborn.

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