Changes in Renal Phosphate Reabsorption in the Aged Rat (44268)

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Abstract. **Depletion of inorganic phosphate (P_i) reserves occurs frequently in aged animals and can result in diminished bone mineralization and osteoporosis. This altered P_i balance results from a reduction in intestinal P_i absorption and an elevation in renal P_i excretion. Since the kidney plays a central role in maintaining P_i homeostasis, we tested whether the increased phosphaturia seen with aging is a consequence of changes in the intrinsic tubular capacity to reabsorb P_i (TmP_i). Male Wistar rats (12-, 18-, and 24-months-old) were acutely thyroparathyroidectomized (TPTX) and prepared for renal clearance studies in the presence and absence of fixed levels of parathyroid hormone (synthetic PTH-(1-34), 1U/kg/min). The maximum capacity for P_i transport (TmP_i) was assessed by infusion of P_i at progressively higher rates (0–6 μmol/min) to increase the filtered load of P_i and facilitate the determination of the TmP_i. TmP_i declined significantly with age (3.51 ± 0.12 vs 3.04 ± 0.19 vs 2.30 ± 0.18 μmol/ml, for 12-, 18-, and 24-month-old rats, respectively, $P < 0.05$) in TPTX rats. Administration of PTH markedly reduced the TmP_i in all age groups. Although the TmP_i attained was similar among the age groups (1.15 ± 0.13 vs 1.15 ± 0.06 vs 1.03 ± 0.09 μmol/ml, for 12-, 18-, and 24-month-old rats, respectively), the magnitude of the reduction in the presence of PTH declined from 67% in 12-month-old rats to 62% and 55% in 18- and 24-month-old rats, respectively. These results demonstrate that aging is associated with a PTH-independent decrease in the intrinsic capacity of the kidney to reabsorb phosphate. Further, the kidney of the aged rat can respond to a pharmacological dose of PTH with appropriate reductions in the TmP_i although the magnitude of the response declines with age.** [P.S.E.B.M. 1998, Vol 218]

Aging is associated with alterations in phosphate (P_i) homeostasis. Serum P_i concentrations are decreased and urinary excretion rates of P_i are elevated in the aged rat (25-month-old) (1, 2), compared with the young (3, 4). The elevated urinary P_i excretion together with reduced intestinal P_i absorption (5) results in a negative P_i balance in the older animal. Since inorganic P_i is a main constituent of the bone matrix and is required for proper bone mineralization, depletion of P_i in the aging animal can disrupt bone homeostasis and may promote and/or accelerate the onset of osteoporosis. Circulating hormones known to influence the extracellular levels of P_i have been shown to change with age (1, 6–8). For example, immunoreactive parathyroid hormone (iPTH) is elevated in the senescent animal (1, 8), whereas circulating levels of 1,25-dihydroxyvitamin D_3 are significantly lower (1, 6) compared to the immature, developing animal. Advancing age has also been shown to cause a decrease in both the pituitary secretion of growth hormone (GH) and circulating serum levels of insulin-like growth factor-I (IGF-I) (9), which are known to enhance the tubular reabsorption of P_i.

Aging also affects various morphological, hemodynamic and functional aspects of the kidney. By age 70 in humans, approximately 20% of total kidney size, primarily the cortical region, is lost (10), and by age 80, renal blood flow decreases by approximately 40% (11). Similarly, a progressive decline in proximal tubular length and volume has been noted with aging, as well as a thickening of the Bowman's capsule basement membrane (12) and a significant decline (30%–50%) in glomerular number (13). Anderson *et al.* have shown that glomerular damage initiates atrophy of both afferent and efferent arterioles leading to glomerular sclerosis and decreased glomerular filtration by

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the kidney (14). In adult humans, there is an accelerated rate of nephron loss between the ages of 40 and 80 with a 50% nephron loss by 75 years of age (15). These age-related renal changes have been shown to result in alterations in the tubular solute transport of the remaining nephrons. However, to what extent aging alters the intrinsic tubular capacity to reabsorb P_i (TmP_i) is not well known and is the focus of the present study.

Materials and Methods

Renal clearance studies were performed on male Wistar rats (provided by the Gerontology Research Center, NIH, Baltimore, MD) at 12-, 18-, and 24-months-of-age. The rats were maintained on a normal rat chow diet (Ralston Purina, St. Louis, MO) containing 0.86% phosphate and 1.2% calcium, and food and water were given *ad libitum*. Room temperature was held between 22°–24°C, and rats were provided with a 12-hr-on/12-hr-off light cycle.

On the day of the experiment, the rats were anesthetized by an intraperitoneal injection of Inactin (80–100 mg/kg) (Promonta, Hamburg, FRG) and prepared for acute renal clearance studies. Body temperature was maintained at 37° ± 0.5°C *via* a servo-controlled heat lamp (Yellow Springs Instruments, Yellow Springs, OH) and a thermoregulated table and monitored by a rectal probe. A tracheostomy was performed so that the animals could breathe spontaneously. Catheters were inserted into the jugular vein for infusing solutions, the carotid artery for blood pressure measurement and blood collections, and the bladder for urine collections.

To remove endogenous levels of circulating parathyroid hormone, all rats underwent a thyroparathyroidectomy (TPTX) on the day of the experiment. An FEP_i of <1–2 ± 1% during the control collection period was considered a successful TPTX in the aged animals. Following TPTX, a 2% solution of inulin was infused at a rate of 2% body wt/hr for 90 min to allow the animal to recover and attain a steady state.

Experiments in the Absence of Parathyroid Hormone. Following the 90-min recovery period, a 30-min control urine clearance was collected. Increasing concentrations of P_i (1, 2, 3, and 6 μmol/min) were added to the inulin infusion to increase the filtered load of P_i and facilitate the determination of the TmP_i. P_i infusions proceeded for 20 min before sequential 30-min clearance periods began. Blood samples were obtained at the midpoint of each clearance period.

Experiments in the Presence of Parathyroid Hormone. In this series, the rats were prepared as previously stated, with the exception that exogenous PTH was administered throughout the experiment. PTH (1-34, Beckman Instruments, Palo Alto, CA) was given in a bolus injection (33 U/kg) iv, and followed with a sustained infusion of 1 U/kg/min for the duration of the experiment.

Analysis. Inulin concentrations in plasma and urine were determined by the anthrone method (16), and GFR was equated with the clearance of inulin. P_i concentrations were measured by the phosphomolybdate method (17). Reabsorbed P_i (R_{Pi}) was calculated as the difference between the amount of P_i filtered ($FL_{Pi} = P_{Pi} \times GFR$), and the amount of P_i excreted ($U_{Pi}V$). The maximum capacity of P_i reabsorption normalized by the GFR (TmP_i) was calculated as the mean of the highest values of R_{Pi}/GFR for each animal within a group. All values are expressed as means ± SE. A one-way analysis of variance followed by Scheffe tests were used for comparisons between groups. Paired Student *t* tests were used to make statistical comparisons within groups.

Results

Experiments in the Absence of Parathyroid Hormone. Mean arterial blood pressure (MAP) was not significantly different between groups (136 ± 4 vs 130 ± 6 vs 127 ± 4 mmHg for 12-, 18-, and 24-month-old rats, respectively) and was maintained throughout the experiment. Table I provides indices of renal function in TPTX animals in the absence of parathyroid hormone. From 12- to 18-months-of-age, there were significant ($P < 0.05$) decreases in the basal plasma P_i concentration (2.22 ± 0.24 vs 1.26 ± 0.13 m*M* for 12- and 18-month-old rats, respectively) and GFR (3.33 ± 0.37 vs 1.48 ± 0.21 ml/min for 12- and 18-month-old rats, respectively). Moreover, while the plasma P_i concentration was stable between 18 and 24 months, aging was associated with a progressive decline in GFR.

Infusions of P_i caused a progressive elevation of the plasma P_i levels that increased the filtered load of P_i, although the GFR remained relatively constant within each age group. The increase in filtered load of P_i caused an elevation in the reabsorption of P_i, but also in the fractional excretion of P_i (FE_{Pi}). Figure 1 depicts this relationship, showing the progressive rise in the fractional excretion of P_i when the plasma P_i concentrations increased. The curve shifted further to the left as age increased indicating an age-related increase in sensitivity to the phosphaturic effect of P_i infusion. This change is likely explained by an age-related reduction in tubular P_i reabsorption. As shown in Figure 2, the TmP_i was significantly ($P < 0.05$) lower in the older animals (3.04 ± 0.19 and 2.30 ± 0.18 μmol/ml for 18- and 24-month-old rats, respectively) compared to the 12-month-old adult rats (3.51 ± 0.12 μmol/ml). The further decrease in TmP_i between 18- and 24-month-old rats was not due to a decrease in food intake (12.0 ± 1.3 vs 11.5 ± 1.4 g/day, respectively, n.s.). Thus, their daily intake of P_i was comparable (~2.5 mmol/day), and in general, should have provided an adequate supply of P_i for the animals. Thus, the intrinsic ability of the kidney to reabsorb P_i (in the absence of PTH) declines precipitously with age.

Experiments in the Presence of Parathyroid Hormone. MAP was no different between age groups (146 ± 5 vs 133 ± 4 vs 152 ± 10 mmHg for 12-, 18-, and 24-month-old rats, respectively) and maintained throughout the experiment. The effects of a pharmacologic dose of PTH

Table I. Effect of Phosphate Infusion in Acutely TPTX Aging Rats

Age	*n*	P_i Infused μmol/min	P_{Pi} m*M*	GFR ml/min	FL_{Pi} μmol/min	FE_{Pi} %	R_{Pi} μmol/ml	R_{Pi}/GFR ml/min
12 month	(5)	0	2.22 ± 0.24	3.33 ± 0.37	7.08 ± 0.91	0.4 ± 0.3	7.04 ± 0.90	2.21 ± 0.24
		1	2.21 ± 0.13	3.56 ± 0.19	7.84 ± 0.67	0.5 ± 0.4	7.81 ± 0.66	2.20 ± 0.13
		2	2.62 ± 0.23	3.05 ± 0.29	8.01 ± 1.22	2.3 ± 1.7	7.83 ± 1.33	2.55 ± 0.23
		3	3.09 ± 0.28	3.56 ± 0.16	11.12 ± 0.97	6.5 ± 1.6	10.60 ± 1.07	2.92 ± 0.31
		6	4.26 ± 0.23	3.83 ± 0.34	16.18 ± 0.91	20.4 ± 1.7	13.51 ± 0.89	3.52 ± 0.14
		6	4.49 ± 0.27	3.10 ± 0.36	14.24 ± 0.87	31.8 ± 2.1	10.50 ± 1.33	3.22 ± 0.31
18 month	(6)	0	1.26 ± 0.13	1.48 ± 0.21	1.82 ± 0.25	2.2 ± 1.0	1.78 ± 0.25	1.24 ± 0.14
		1	2.08 ± 0.11	2.17 ± 0.52	4.50 ± 1.19	16.7 ± 4.7	3.81 ± 1.04	1.75 ± 0.15
		2	3.17 ± 0.28	1.97 ± 0.43	6.10 ± 1.37	33.1 ± 4.7	4.04 ± 0.92	2.24 ± 0.28
		3	5.12 ± 0.19	1.89 ± 0.29	9.42 ± 1.23	49.3 ± 3.5	4.89 ± 0.81	2.58 ± 0.16
		6	6.72 ± 0.42	1.80 ± 0.38	12.02 ± 2.73	68.9 ± 7.5	4.42 ± 1.76	2.52 ± 0.41
		6	8.44 ± 0.84	1.71 ± 0.31	13.40 ± 1.79	72.0 ± 6.8	3.84 ± 1.32	2.39 ± 0.42
24 month	(6)	0	1.34 ± 0.23	1.08 ± 0.19	1.35 ± 0.20	0.2 ± 0.0	1.35 ± 0.20	1.33 ± 0.23
		3	1.77 ± 0.14	1.48 ± 0.19	2.59 ± 0.31	5.0 ± 2.2	2.44 ± 0.26	1.68 ± 0.13
		3	2.31 ± 0.08	1.23 ± 0.27	2.78 ± 0.56	11.5 ± 2.5	2.44 ± 0.49	2.05 ± 0.08
		3	2.62 ± 0.12	1.62 ± 0.21	4.16 ± 0.42	27.6 ± 5.3	3.03 ± 0.38	1.88 ± 0.11
		6	3.05 ± 0.18	1.51 ± 0.15	4.56 ± 0.36	40.5 ± 3.7	2.68 ± 0.20	1.80 ± 0.07
		6	3.48 ± 0.15	1.63 ± 0.21	5.67 ± 0.75	53.6 ± 5.7	2.50 ± 0.30	1.59 ± 0.17
		6	3.55 ± 0.19	1.94 ± 0.16	6.85 ± 0.62	56.9 ± 3.4	2.94 ± 0.35	1.53 ± 0.15

Note. Values are means ± SE; *n,* no. of animals in each group. P_i, phosphate; P_{Pi}, plasma phosphate concentration; FE_{Pi}, fractional excretion of phosphate; FL_{Pi}, filtered load of phosphate; R_{Pi}, absolute phosphate reabsorption; GFR, glomerular filtration rate; TPTX, thyroparathyroidectomized. Statistical comparisons are discussed in text.

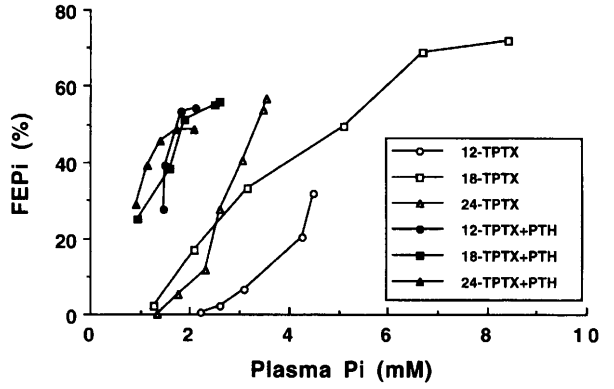

Figure 1. Relationship between fractional excretion of phosphate (FEP_i) and plasma phosphate concentration (Plasma P_i) as a function of age. Data were obtained in thyroparathyroidectomized (TPTX) rats with and without infusion of parathyroid hormone (PTH).

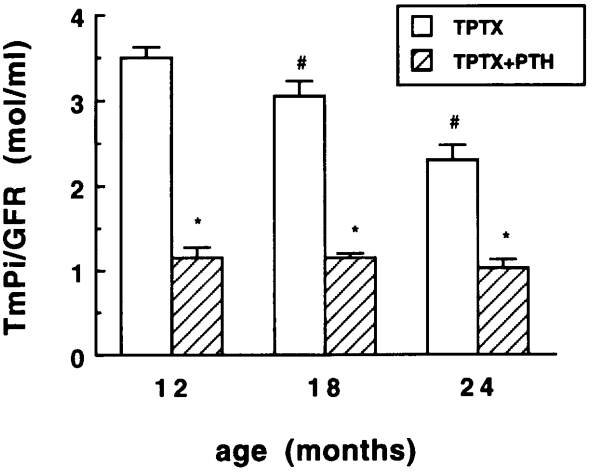

Figure 2. Age-related changes in the maximum capacity of phosphate reabsorption (TmP_i/GFR) in thyroparathyroidectomized (TPTX) rats and in TPTX rats infused with parathyroid hormone TPTX + PTH). Values were determined by averaging highest R_{Pi}/GFR in each animal within an age group. Statistical comparisons are as follows: TPTX 12-month > 18-month > 24-month, $P < 0.05$. No significant difference ($P > 0.05$) was seen between any age group in the presence of PTH. * = means significantly different from TPTX-only aged matched males, # = means significantly different from the 12-month-old age group.

on basal renal function in different aged animals is shown in Table II. In the presence of PTH, basal plasma P_i levels were significantly lower in all age groups when compared to TPTX-only rats (1.50 ± 0.13 and 0.96 ± 0.08 and 0.92 ± 0.06 m*M* vs 2.22 ± 0.24 and 1.26 ± 0.13 and 1.34 ± 0.23 m*M* in 12-, 18-, and 24-month-old rats, respectively, $P < 0.05$). Further, a significant ($P < 0.05$) age-related decline was evident in both basal plasma P_i concentration and GFR from 12- to 18-months-of-age although there were no differences between the senescent groups (18- vs 24-months-of-age).

Infusion of P_i, in the presence of PTH, resulted in smaller increases in plasma P_i concentrations and filtered load of P_i (Table II), compared to P_i infusions in the absence of PTH (Table I). This was due to the much higher basal rates of urinary P_i excretion seen in the presence of PTH. However, the phosphaturic response to P_i infusion in the presence of PTH was enhanced in all groups (Figure 1). Although FE_{Pi}, in the presence of PTH, was significantly ($P < 0.05$) higher in all age groups compared to TPTX-only group, there was no age-related differences. The increased P_i excretion was associated with a marked decrease in TmP_i (Fig. 2). In fact, PTH reduced the TmP_i to similar levels between the different age groups (1.15 ± 0.13 vs 1.15 ± 0.06 vs 1.03 ± 0.09 μmol/ml, for 12-, 18- and 24-month-old rats,

Table II. Effect of Phosphate Infusions in Acutely TPTX Aging Rats in the Presence of PTH

Age	*n*	P_i Infused μmol/min	P_{Pi} m*M*	GFR ml/min	FL_{Pi} μmol/min	FE_{Pi} %	R_{Pi} μmol/ml	R_{Pi}/GFR μmol/min
12 month	(5)	0	1.50 ± 0.13	3.90 ± 0.31	5.82 ± 0.75	27.6 ± 3.6	4.25 ± 0.04	1.90 ± 0.13
		1	1.48 ± 0.11	3.83 ± 0.51	5.61 ± 0.82	39.0 ± 4.8	3.56 ± 0.06	0.93 ± 0.12
		2	1.83 ± 0.11	2.91 ± 0.43	5.03 ± 0.61	53.4 ± 3.5	2.53 ± 0.04	0.87 ± 0.09
		3	2.13 ± 0.16	3.07 ± 0.79	6.11 ± 1.51	54.2 ± 3.5	2.98 ± 0.06	0.97 ± 0.08
18 month	(6)	0	0.96 ± 0.08	1.56 ± 0.24	1.49 ± 0.23	24.8 ± 5.3	1.17 ± 0.23	0.74 ± 0.08
		1	1.58 ± 0.15	1.83 ± 0.16	2.87 ± 0.40	38.3 ± 6.2	1.74 ± 0.29	0.94 ± 0.11
		2	1.90 ± 0.24	2.44 ± 0.29	4.71 ± 0.87	51.2 ± 7.2	2.22 ± 0.50	0.88 ± 0.13
		3	2.52 ± 0.22	1.70 ± 0.26	4.18 ± 0.53	54.9 ± 7.2	1.41 ± 0.05	0.93 ± 0.15
		3	2.61 ± 0.25	2.04 ± 0.12	5.24 ± 0.38	55.8 ± 9.1	1.59 ± 0.16	0.88 ± 0.12
24 month	96)	0	0.92 ± 0.06	1.74 ± 0.18	1.57 ± 0.13	28.9 ± 8.1	1.12 ± 0.17	0.66 ± 0.09
		1	1.14 ± 0.08	2.27 ± 0.26	2.59 ± 0.38	39.1 ± 3.3	1.58 ± 0.25	0.69 ± 0.06
		2	1.40 ± 0.09	2.66 ± 0.18	3.71 ± 0.29	45.8 ± 4.3	2.02 ± 0.25	0.77 ± 0.09
		3	1.74 ± 0.13	2.10 ± 0.27	3.66 ± 0.48	48.5 ± 4.7	1.88 ± 0.34	0.92 ± 0.14
		3	2.08 ± 0.10	1.76 ± 0.32	3.71 ± 0.78	48.6 ± 5.8	1.94 ± 0.56	0.94 ± 0.10

Note. Values are means ± SE; *n*, no. of animals in each group. Abbreviations are as described in Table I.

respectively) although the magnitude of the reduction, in the presence of PTH, declined from 67% in 12-month-old rats to 62% and 55% in 18- and 24-month-old rats, respectively.

Discussion

The present study demonstrates a progressive PTH-independent, age-related decline in the intrinsic capacity of the renal tubule to reabsorb P_i. Further, despite the lower TmP_i, the aged kidney still responds to PTH with a marked reduction in TmP_i, although the magnitude of the response declines with age. These findings, together with the known elevations in circulating PTH levels in the aged animal, may explain the hypophosphatemia observed in senescence.

There are several potential factors that may contribute to the changes observed in whole kidney P_i reabsorption in aging animals. Aging is associated not only with nephron loss primarily from the juxtamedullary region (12), but also with changes in proximal tubular cells, such as decreased mitochondria number (18) and reduced basolateral Na^+-K^+ activated ATPase activity (19). Since P_i uptake utilizes the Na^+ gradient generated by the basolateral Na^+/K^+ ATPase pump, a reduction in the activity of this pump would limit the ability of the proximal tubule to reabsorb P_i. Previous studies have also demonstrated that the maximum capacity for P_i reabsorption is greater in proximal tubules from deep as compared to superficial nephrons (20). Therefore, the combination of a selective juxtamedullary nephron loss, along with a reduction in the ability of the remaining proximal tubular cells to generate a sodium gradient, may contribute, in part, to the diminished ability of the aged kidney to reclaim the filtered load of P_i.

Sodium-dependent phosphate (Na-P_i) transport on the luminal surface of the proximal tubule is the rate limiting step by which P_i is reabsorbed. Using renal brush-border membrane vesicle (BBMV) preparations, Kiebzak and Sacktor reported an age-dependent decline in the V_{max} of P_i transporters without a decrease in the affinity (K_m) for P_i. This suggested that aging is associated with either a decrease in the number of P_i carriers or a decrease in the transporter turnover rate in the proximal tubule (21). Recently, Sorribas *et al.* have determined that both NaP_i-2 mRNA level and protein abundance is decreased in the BBM of proximal tubules from aged (12- to 16-month-old) rats compared to young adult (3- to 4-month-old) rats (22). Whether changes are present in other nephron segments is still unknown.

Alterations in the chemical composition of the lipid bilayer have also been shown to influence the function of both passive and carrier-mediated transport systems located on the cell membrane (23–25). Several laboratories have demonstrated that there is an age-related increase in the cholesterol, sphingomyelin, and phosphatidylinositol content of brush border membranes causing a decrease in membrane fluidity (26–28), which may affect Na-P_i co-transport from the proximal tubule (29–32). Molitoris *et al.* report that the significant increase in the V_{max} of the Na-P_i co-transport, during dietary P_i restriction, is due to a reduction in BBM cholesterol content and increased fluidity (32). More recently, using 24-month-old Fischer 344 rats, the elevated phosphaturia was associated with increases in cortical BBM cholesterol and sphingomyelin content and decreased BBM fluidity (26). Hence, a decline in the number of BBM Na-P_i transporters, in addition to an age-related increase in membrane stiffness, may be an important factor contributing to the lower renal reabsorption of P_i in aging.

In this study, the age-related decline in TmP_i was found to be independent of PTH. Several humoral factors have been shown to affect the intrinsic renal P_i reabsorption and may contribute to the age-related reduction in TmP_i. The GH/IGF-I axis is known to affect the reabsorption of P_i in a positive fashion, since chronic treatment with GH enhances tubular reabsorption of P_i (33, 34), and TmP_i is significantly reduced in hypophysectomized adult rats (35). The primary effects of growth hormone on renal P_i retention are thought to be mediated through hepatic IGF-I (36). Since circulating levels of both GH and IGF-I decline with age (9, 37), this

could potentially contribute to the increased phosphaturia seen with aging.

In the present study, although the aged rat responded to PTH with an elevation in P_i excretion and an appropriate reduction in TmP_i, the magnitude of the response was less compared to younger adult rats. The decline in the PTH response with age may be due to the increased circulating levels of PTH, perhaps as a consequence of reduced renal clearance of PTH (38, 39), which may lead to downregulation of renal PTH receptors. Marcus and Gonzales reported that PTH-stimulated cAMP production is attenuated in cortical renal slices from 12-month-old rats compared to slices from 2-month-old rats (40), whereas Armbrecht *et al.* demonstrated a decline in the PTH-induced $1,25\text{-}(OH)_2D_3$ synthesis in 13-month-old rats compared to 2-month-old rats (41). These findings suggest that the aged kidney may possess a degree of end-organ insensitivity toward the phosphaturic and vitamin D_3-stimulating effects of PTH. On the other hand, the lower magnitude of response may reflect the reduced GFR and plasma P_i concentration, and the already higher rate of urinary P_i excretion. In the absence of a dose-response study, it is not possible to determine changes in the sensitivity of the renal tubule to PTH.

In conclusion, the present study demonstrates a significant age-related decrease in the tubular capacity to reclaim the filtered load of P_i that is independent of the effects of PTH. In addition, it appears that the aging kidney can still respond to the phosphaturic effect of PTH, although there may be some degree of insensitivity with aging. Interestingly, the decline in TmP_i seen throughout senescence is consistent with that seen previously, as the highest capacity to reabsorb phosphate occurred in the immature (3- to 4-week-old) rat and progressively declined toward adulthood (52-week-old rat) (4).

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