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Parathyroid hormone-independent adaptation of the renal handling of phosphate in response to renal mass reduction

JOSEPH CAVERZASIO, HANS-JAKOB GLOOR, HERBERT FLEISCH, and JEAN-PHILIPPE BONJOUR

Department of Pathophysiology, University of Berne, Murtenstrasse 35, 3010 Berne, Switzerland

Parathyroid hormone-independent adaptation of the renal handling of phosphate in response to renal mass reduction. In man as well as in experimental animals progressive renal failure is associated with a decrease in the fractional reabsorption (FR) of inorganic phosphate (P_i). This response has been considered as an adaptation phenomenon and generally attributed to an increase in parathyroid hormone (PTH) secretion. One report indicates that in chronic thyroparathyroidectomized (TPTX) dogs treated with large doses of vitamin D progressive renal failure can also be associated with a fall in FRP_i. However, in this latter study the concomittant administration of vitamin D could have accounted for the observed decrease in FRP_i. In our study we investigated whether or not chronic reduction in renal mass leads to a similar decrease in maximal net tubular P_i reabsorption per volume of glomerular filtrate (maximal TRP_i/ml GF) in the presence and absence of PTH and without pharmacological supplementation in vitamin D. Male rats were either TPTX or sham-operated (intact). One and two weeks later the animals of both groups were either subtotally nephrectomized (NX) in two stages or sham-operated (control). Four weeks after the second renal operation, the glomerular filtration rate (GFR) and the reabsorption of P_i were determined by clearance methodology under acute sodium chloride and P_i infusion, that is, at endogenous and increased plasma P_i concentrations ($[P_i]_{Pl.}$). Thus maximal TRP_i/ml GFR could be determined. In rats with intact parathyroid glands GFR was 1.56 ± 0.10 (mean ± SEM) and 0.54 ± 0.10 ml/min in control and NX respectively, whereas maximal TRP_i/ml GF was 2.24 ± 0.07 in control and 1.57 ± 0.18 μmol/ml ($P < 0.005$) in NX. In TPTX rats GFR was 1.66 ± 0.27 and 0.62 ± 0.06 ml/min in control and NX respectively, whereas maximal TRP_i/ml GF was 3.80 ± 0.20 in control and 2.95 ± 0.13 μmol/ml ($P < 0.005$) in NX. The marked decrease in maximal TRP_i/ml GF observed in TPTX after subtotal NX could not be ascribed to any consistent change in plasma calcium. Our study provides conclusive evidence that the decrease in maximal TRP_i/ml GF in response to renal mass reduction can occur to the same degree in the presence or absence of PTH.

Adaptation indépendente de l'hormone parathyroïdienne du comportement rénal du phosphate en réponse à la réduction de la masse rénale. Chez l'homme de même que chez l'animal d'expérience l'insuffisance rénale progressive est associée à une diminution de la réabsorption fractionnelle (FR) du phosphate inorganique (P_i). Cette réponse a été considérée comme un phénomène d'adaptation et est généralement attribuée à une augmentation de la sécrétion d'hormone parathyroïdienne (PTH). Un travail indique que chez le chien en état de thyroparathyroïdectomie chronique (TPTX) traité par de larges doses de vitamine D, l'insuffisance rénale progressive peut aussi être associée à une diminution de FRP_i. Cependant, dans ce dernier travail, l'administration concomitante de vitamine D peut avoir eu pour conséquence la diminution observée de FRP_i. Dans le présent travail nous avons recherché si en présence ou en l'absence de PTH et sans supplémentation pharmacologique en vitamine D la réduction chronique de la masse rénale détermine une diminution semblable de la réabsorption maximale nette tubulaire de phosphate par unité de filtrat glomérulaire (max.TRP_i/ml GF). Des rats males ont été soit thyroparathyroïdectomisés soit soumis à un simulacre d'opération. Une puis deux semaines plus tard, les animaux des deux groupes ont été soit soumis à une néphrectomie subtotale (NX) en deux étapes, soit soumis à un simulacre d'intervention (contrôles). Quatre semaines après la deuxième intervention rénale, le débit de filtration glomérulaire (GFR) et la réabsorption de P_i ont été déterminés par la méthode des clearances sous perfusion aiguë de chlorure de sodium et de P_i, c'est-à-dire aux concentrations plasmatiques de P_i endogène et augmentées ($[P_i]_{Pl.}$). Ainsi on a pu déterminer max.TRP_i/ml GF. Chez les rats dont les glandes parathyroïdes sont intactes, GFR était de 1,56 ± 0,10 (moyenne ± SEM) et 0,54 ± 0,10 ml/mn chez les contrôles et les NX respectivement alors que max.TRP_i/ml GF était de 2,24 ± 0,07 chez les contrôles et de 1,57 ± 0,18 μmol/ml ($P < 0,005$) chez NX. Chez les rats TPTX GFR était de 1,66 ± 0,27 et 0,62 ± 0,06 ml/mn chez les contrôles et NX respectivement, alors que max.TRP_i/ml GF était 3,80 ± 0,20 chez les contrôles et 2,95 ± 0,13 μmol/ml ($P < 0,005$) chez NX. La diminution importante de max.TRP_i/ml GF observée chez TPTX après NX ne peut pas être attribuée à une modification importante du calcium plasmatique. En conclusion, notre travail apporte des preuves importantes de ce que la diminution de max.TRP_i/ml GF en réponse à la réduction de la masse rénale peut survenir de la même façon en présence ou en l'absence de PTH.

The fraction of filtered inorganic phosphate (P_i) reabsorbed declines as the number of residual nephrons diminishes in the course of progressive renal disease [1–4]. This alteration is not merely explained by an increase in the plasma P_i concentration ($[P_i]_{Pl.}$) and/or in the glomerular filtration rate (GFR) per nephron [2, 3], although this latter factor may play a contributing role [5]. It can be dissociated from the decrease in the fractional reabsorption of sodium [6] which also occurs in progressive renal failure [4]. It has been interpreted as a homeostatic adjustment of the tubular P_i transport, thus allowing the maintenance of the P_i balance of the organism [2–4]. Parathyroid hormone (PTH) has been considered the key factor in the efferent limb of the system controlling P_i homeostasis in progressive renal failure [2]. This belief is based on the following observations made in experimental or clinical chronic renal failure: *(1)* The usual occurrence of a progressive elevation of plasma radioimmunoassayable PTH [7, 8]; *(2)* the demonstration of a rise in the fractional reabsorption of P_i after removal of the parathyroid glands [2] or after reducing PTH activity by lowering the P_i intake [8, 9]. When considered separately none of these observations represents direct evidence for a key role

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of PTH in the apparent tubular adaptation to nephron loss. This finding is particularly true for the increased P_i reabsorption after parathyroidectomy or low phosphorus diet because the same response is observed in animals or man with intact renal mass. Nevertheless, when taken together, these observations are certainly suggestive in pointing to PTH as a possible effector element of the P_i control system in progressive renal failure. Conclusive evidence about the prevailing and unique role of PTH, however, should be based on the demonstration that in the absence of the parathyroid glands the decrease in P_i reabsorption does not take place, or at least is considerably attenuated. A study performed by Swenson et al [10] would suggest that the tubular P_i adaptation is preserved in uremic thyroparathyroidectomized dogs supplemented with large doses of vitamin D. However, in our study [10] it remains uncertain whether or not the observed decrease in P_i reabsorption was due to the pharmacological doses of vitamin D [11–13] which were administered to the uremic thyroparathyroidectomized dogs.

A PTH-independent adaptation of the renal handling of P_i to variations in the P_i supply [14–16] and requirements [16–18] has been described recently. That a PTH-independent mechanism might also play an important role in the adaptive response to nephron loss remained a possibility which had not yet been explored adequately. In our investigation this possibility has been considered by studying the influence of renal mass reduction on the renal handling of P_i in chronically thyroparathyroidectomized rats. We removed the parathyroid glands several days before reducing the renal mass to rule out the possibility that PTH could induce the adaptive response. The study was performed in animals which did not receive previously any pharmacological supplement of vitamin D and of which the prior food, and thus P_i intake, was controlled strictly.

Methods

Preparation of the animals. Male Wistar rats, weighing 160 to 180 g and raised on a commercial chow food (Altromin 1314) containing 1.2 g/100 g phosphorus, 1.1 g/100 g calcium, and 180 IU/100 g vitamin D_3, were selected for the study.

On day 1 the animals were either surgically thyroparathyroidectomized (TPTX) or sham-operated (SHAM) as described previously [19]. On day 3 the adequacy of parathyroid gland removal was checked by determining the plasma calcium concentration ($[Ca]_{Pl}$). Only TPTX rats with $[Ca]_{Pl}$ lower than 2.0 mM were kept in the study. From day 4 all selected TPTX and SHAM animals ate 15 g of the above mentioned lab chow daily. They were allowed to drink distilled water ad libitum. TPTX animals received from day 4 to the end of the experiments 2 μg of L-Thyroxine (Fluka AG, Buchs, Switzerland) s.c. three times a week, while SHAM rats received an equivalent volume of the solvent vehicle (0.2 ml of 0.15 M sodium chloride).

On day 7 the first stage of the procedure of renal mass reduction was accomplished under pentobarbital anesthesia through a lumbar incision by resecting the two poles of the left kidney and cauterizing the remainder of its surface. We applied this procedure to half the TPTX and the SHAM rats, while we operated on the remaining animals, designated as controls, making skin and muscle incisions above the left kidney. On day 14 the second stage of the renal mass reduction procedure was performed under light ether anesthesia by removing the right kidney of the TPTX and SHAM rats which had one week before experiencing the partial nephrectomy on the left side. We pseudo-operated on the control TPTX and SHAM animals in the right kidney area.

From day 42 to day 49, that is, during the 8 days preceding the clearance experiments, all rats were fed with 15 g/day of a diet (Altromin C1034) containing 0.8 g/100 g phosphorus and 1.1 or 0.7 g/100 g calcium. This diet was deficient in vitamin D. Therefore, in order to maintain a normal vitamin D status, 10 IU of cholecalciferol dissolved in 0.2 ml of vegetable oil was added to the daily ration of each rat. The daily ration was distributed between 9 and 10 A.M. On day 48, that is, 2 days before the clearance experiments, a subtotal cystectomy under light ether anesthesia was made in the four groups of rats as described previously [19].

Clearance experiments. The general clearance methodology for assessing the renal handling of P_i in conscious rats has been described earlier [19]. In our study the experiments were started between 8 and 9 A.M. and lasted until 3 to 4 P.M. A first dose of 0.4 μC of [methoxy-^{3}H]inulin (New England Nuclear, Boston, Massachusetts) and 12.8 mg of unlabelled inulin (Fluka AG, Buchs, Switzerland) dissolved in isotonic saline was injected i.v. in a volume of 0.4 ml per rat. An 0.15 M sodium chloride solution containing 50 μC/100 ml of [methoxy-^{3}H]-inulin and 1 g/100 ml of unlabelled inulin was then infused at a rate of 4 ml/hr into a tail vein throughout the experiment. After an equilibration period of 90 min, a first clearance period was made by collecting urine samples for 30 min and sampling blood at the end of this period. The 0.15 M sodium chloride solution was then replaced by isotonic solutions containing inorganic phosphate (P_i), at concentrations calculated to deliver 1, 2, and 3 μmol/min. The pH of these solutions was 7.4. It was obtained by adding in adequate proportion monobasic sodium phosphate and dibasic sodium phosphate. The osmolality of the P_i solutions was adjusted to 300 to 310 mOsm/liter by the addition of sodium chloride where necessary. During each P_i infusion, a 30-min urine collection was made after a 45-min equilibration period. Blood samples were taken at the end of each clearance period.

In an additional experiment TPTX rats with intact or reduced renal mass were infused i.v. with the 0.15 M sodium chloride solution throughout the experiment. This solution was infused at slow (2 ml/hr) and rapid (8 ml/hr) rate. The clearances of [methoxy-^{3}H]-inulin, P_i and sodium were determined under each infusion rate after a 90-min equilibration period.

Analytical methods. The activity of ^{3}H-inulin in plasma and urine samples was counted in a liquid scintillation spectrometer. Calcium was measured by complexometric titration with EGTA (Corning Calcium Analyzer 940) and sodium by flame photometry. P_i was determined spectrophotometrically as phosphomolybdate after reduction with a 10% ascorbic acid solution. The calcium and phosphorus content of the diets was analyzed after the incineration of 1 g dry weight aliquots and dissolution of the ash in 0.1 N hydrochloric acid.

Statistical analysis. The experimental data are expressed as mean values ± standard error of the mean (SEM). The significance of the differences between groups was assessed by the two-sided Student's *t* test.

Results

The effect of subtotal nephrectomy on the renal handling of P_i of rats with (SHAM) and without (TPTX) parathyroid hormone

Table 1. Influence of subtotal nephrectomy on the renal handling of P_i in rats with (SHAM) and without thyroparathyroid glands (TPTX)[a]

Infused P_i *μmol/min*	C_{IN} *ml/min*	$[P_i]_{PI}$ *mM*	$U_{P_i}V$ *μmol/ml GF*	TRP_i *μmol/ml GF*	$[Ca]_{PI}$ *mM*	FE_{NA} *%*
SHAM Intact renal mass (N = 6)						
0	1.56	2.22	0.069	2.153	2.28	1.53
	±0.10	±0.08	±0.014	±0.072	±0.04	±0.18
1	1.79	2.62	0.529	2.088	2.27	2.60
	±0.12	±0.04	±0.051	±0.073	±0.04	±0.32
2	1.78	2.84	0.983	1.653	2.06	4.11
	±0.18	±0.10	±0.183	±0.091	±0.06	±0.24
3	1.89	3.23	1.906	1.323	2.10	4.43
	±0.17	±0.09	±0.090	±0.128	±0.05	±0.24
Subtotal nephrectomy (N = 5)						
0	0.54	2.25	0.791	1.199	2.49	2.72
	±0.10	±0.06	±0.192	±0.227	±0.08	±1.03
1	0.51	2.62	1.323	1.307	2.21	2.90
	±0.07	±0.03	±0.196	±0.170	±0.04	±0.90
2	0.55	3.46	2.354	1.102	2.18	4.41
	±0.01	±0.13	±0.088	±0.150	±0.09	±1.35
3	0.57	4.62	3.693	1.135	2.00	6.01
	±0.07	±0.18	±0.329	±0.355	±0.09	±1.58
TPTX Intact renal mass (N = 6)						
0	1.66	3.54	0.084	3.453	1.48	1.24
	±0.27	±0.06	±0.024	±0.074	±0.08	±0.38
1	1.43	4.16	0.399	3.759	1.33	3.55
	±0.12	±0.17	±0.089	±0.238	±0.08	±0.42
2	1.18	4.80	1.138	3.656	1.23	4.48
	±0.12	±0.25	±0.060	±0.247	±0.09	±0.19
3	1.38	5.27	2.110	3.158	1.11	5.55
	±0.12	±0.20	±0.100	±0.141	±0.06	±0.53
Subtotal nephrectomy (N = 6)						
0	0.62	2.70	0.547	2.153	1.71	2.76
	±0.06	±0.04	±0.059	±0.082	±0.05	±0.49
1	0.63	3.37	0.783	2.588	1.59	4.99
	±0.03	±0.08	±0.049	±0.124	±0.06	±0.28
2	0.55	4.41	1.693	2.718	1.34	6.38
	±0.04	±0.12	±0.126	±0.076	±0.05	±0.73
3	0.51	5.60	2.757	2.846	1.22	6.91
	±0.05	±0.10	±0.132	±0.136	±0.03	±0.76

[a] Values represent means ± SEM; *n* represents the number of animals. Abbreviations used are defined: C_{IN}, clearance of inulin; $[P_i]_{PI}$, phosphatemia; $U_{P_i}V$, urinary excretion of P_i; TRP_i, net tubular reabsorption of P_i; $[Ca]_{PI}$, calcemia; FE_{NA}, fractional excretion of sodium. Animals were sham-operated (SHAM) or thyroparathyroidectomized (TPTX) 50 days before the clearance study. The reduction in the renal mass was made in two steps, 36 and 42 days, before the clearance study. During the last 8 days, the rats were pair-fed with a diet containing 0.8 g/100 g phosphorus and 1.1 g/100 g calcium. The mean (± SEM) body wt of the animals with intact renal mass was 219 ± 2 and 198 ± 4 in SHAM and TPTX, respectively, that of the subtotally nephrectomized rats was 228 ± 10 and 209 ± 2 in SHAM and TPTX, respectively.

is presented in Table 1 and in Figures 1 and 2. The procedure used for reducing the renal mass in these experiments led to a 60 to 70% decrease in the GFR as assessed by the clearance of inulin (Table 1). As expected in SHAM rats, the reduction in the renal mass was associated (Table 1) with an increase in the urinary P_i excretion per unit volume of glomerular filtrate ($U_{P_i}V$/ml GF). Removal of the thyroparathyroid glands before inducing the renal failure did not attenuate this process. Indeed in TPTX rats $U_{P_i}V$/ml GF was much larger in subtotally nephrectomized (NX) animals than in control counterparts. In NX rats the fractional excretion of sodium (FE_{NA}) during the first period of clearance was about twice the excretion recorded in the control groups. Removal of the parathyroid glands did not affect FE_{NA} significantly (Table 1). An increase in FE_{NA} occurred in all groups during the course of the experiment. In SHAM or TPTX rats with a reduced renal mass the rise in FE_{NA} was not accompanied by a fall in the tubular reabsorption of P_i (Table 1). Figure 1 depicts the relationship between the plasma P_i concentration ($[P_i]_{PI}$) and the fractional excretion (FE) of P_i in the four experimental groups. In SHAM rats, FEP_i was markedly elevated in NX animals within a $[P_i]_{PI}$ range from 2.2 to 2.7 mM. The difference in FEP_i between SHAM-control and SHAM-NX diminished progressively when $[P_i]_{PI}$ was raised above 2.7 mM. In TPTX rats FEP_i was much greater in NX animals than in controls within a $[P_i]_{PI}$ range from 3.4 to 4.2 mM. Above this value the difference in FEP_i diminished progressively. Thus in TPTX as in SHAM animals the elevation of FEP_i with increasing $[P_i]_{PI}$ in response to an acute P_i infusion appears to be less pronounced in the presence of a reduced rather than an intact renal mass.

Figure 2 shows the maximal net tubular P_i reabsorption (maximal TRP_i/ml GF) measured in the four experimental groups. The data were obtained by averaging the values determined in each rat. Because the individual maximal TRP_i/ml GF was not always observed during the same clearance period, the averaged values presented on Figure 2 can slightly differ from the highest means given in Table 1. As depicted in Figure 2, reduction in renal mass (NX) in SHAM rats was associated with

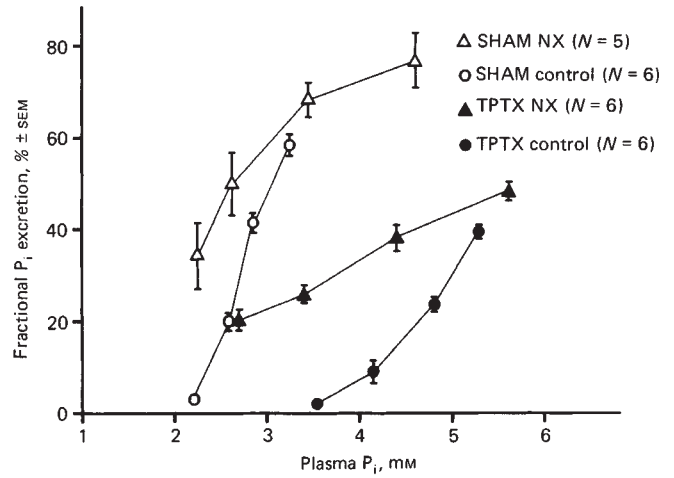

Fig. 1. *Effect of subtotal nephrectomy (NX) on the renal handling of P_i in sham-operated (SHAM) and thyroparathyroidectomized (TPTX) rats.* The fractional excretion of P_i was measured at various plasma phosphorous concentrations during the infusion of sodium chloride and sodium phosphate solutions (see details in **Methods**). SEM are drawn only when larger than the symbol representing the mean.

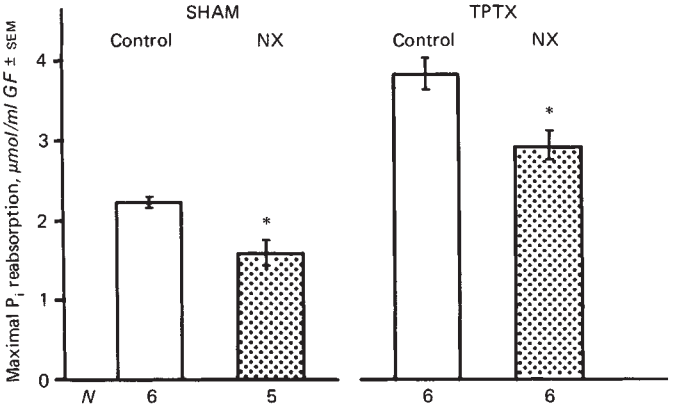

Fig. 2. *Effect of subtotal nephrectomy (NX) on the maximal P_i reabsorption in sham-operated (SHAM) and thyroparathyroidectomized (TPTX) rats.* Each column corresponds to the mean of the highest individual values of TRP_i/ml GF determined during the clearance study presented in Table 1. *Asterisk* denotes $P < 0.001$ compared with the respective control group.

a significant decrease in maximal TRP_i/ml GF ($\Delta = -0.67$ μmol/ml). In TPTX rats the decrease in maximal TRP_i/ml GF ($\Delta = -0.85$ μmol/ml) was, if anything, greater than in SHAM animals. Figure 2 also shows that the influence of thyroparathyroidectomy on maximal TRP_i/ml GF was not more pronounced in NX animals than in those with an intact renal mass. Differences in basal plasma calcium between SHAM and TPTX rats with a normal renal mass on the one hand, and between SHAM and TPTX rats with reduced renal mass on the other, were almost identical, 0.80 mM and 0.78 mM respectively (Table 1, first period of clearance).

Chronic elevation of plasma calcium has been shown to be associated with a decrease in maximal TRP_i/ml GF in TPTX rats [20]. In the TPTX animals fed a 1.1 g/100 g calcium diet, the initial plasma calcium was slightly, but significantly, higher in NX as compared to the group with intact renal mass (1.71 ± 0.05 versus 1.48 ± 0.08 mM, $P < 0.05$, Table 1, first period of clearance). Therefore, another experiment was carried out in TPTX rats fed a 0.7 g/100 g calcium and 0.8 g/100 g phosphorus diet. Reduction of the renal mass in these animals was not associated with a rise in plasma calcium (Table 2). Nevertheless, the decrease in maximal TRP_i/ml GF took place (Table 2) to the same extent as in the former experiment.

Table 2. Influence of subtotal nephrectomy on the plasma calcium and maximal P_i reabsorption of TPTX rats fed a 0.7 g/100 g calcium and 0.8 g/100 g phosphorus diet[a]

	Intact renal mass	Subtotal nephrectomy
C_{IN}, *ml/min*	1.69 ± 0.18	0.69 ± 0.07[b]
$[Ca]_{PI}$, *mM*	1.40 ± 0.06	1.41 ± 0.06
Maximal P_i reabsorption, *μmol/ml GF*	3.80 ± 0.12	2.79 ± 0.09[b]
N	6	5

[a] Values are the mean ± SEM; *N* represents the number of animals. Abbreviations used are: C_{IN}, clearance of inulin; $[Ca]_{PI}$, calcemia; maximal P_i reabsorption, highest value of tubular P_i reabsorption per ml of glomerular filtrate determined during a clearance study identical to that presented in Table 1 and Figures 1 and 2.

[b] $P < 0.001$ as compared to the group with intact renal mass.

Finally, an additional experiment was made in order to assess whether or not the difference in the renal handling of P_i between TPTX-NX and TPTX-control rats could result because more acute extracellular expansion occurs in the former group. Figure 3 shows that the increase in FEP_i associated with the decrement in $[P_i]_{PI}$ in TPTX-NX as compared to TPTX-control rats remained virtually identical whether or not the determination of the renal handling of P_i was made under a very slow (2 ml/hr) or a rapid (8 ml/hr) isotonic infusion rate. Thus, in TPTX-NX rats a fourfold increase in FE_{NA} promoted by acute extracellular volume expansion did not modify significantly the renal handling of P_i (Fig. 3).

Discussion

The present work demonstrates that in the chronic absence of parathyroid glands an increase in the fractional excretion of P_i (FEP_i) does occur in the remaining nephrons of subtotally nephrectomized rats. In TPTX, as in SHAM rats, the influence of reducing the renal mass on FEP_i cannot be ascribed to an increased plasma P_i concentration (Fig. 1). The increased FEP_i observed after subtotal nephrectomy is associated with a significant reduction in the maximal net P_i reabsorption per volume of glomerular filtrate (maximal TRP_i/ml GF) in both TPTX and SHAM animals. Of prime importance is the fact that the decrease in maximal TRP_i/ml GF is of the same magnitude in TPTX as in SHAM animals. Furthermore, in TPTX it can be observed in the absence of a change in plasma calcium.

Acute extracellular volume expansion (ECVE) is one maneuver which can increase the fractional excretion of P_i [21]. Although the phosphaturic response of the acute ECVE has been reported to be blunted in the absence of PTH [22], this factor may have contributed to the increased FEP_i observed (Fig. 1) in the remnant kidney of TPTX rats. However, the experiment presented in Figure 3 would prefer ruling out the possibility that acute ECVE could have played an important role in the change in the renal handling of P_i monitored in TPTX

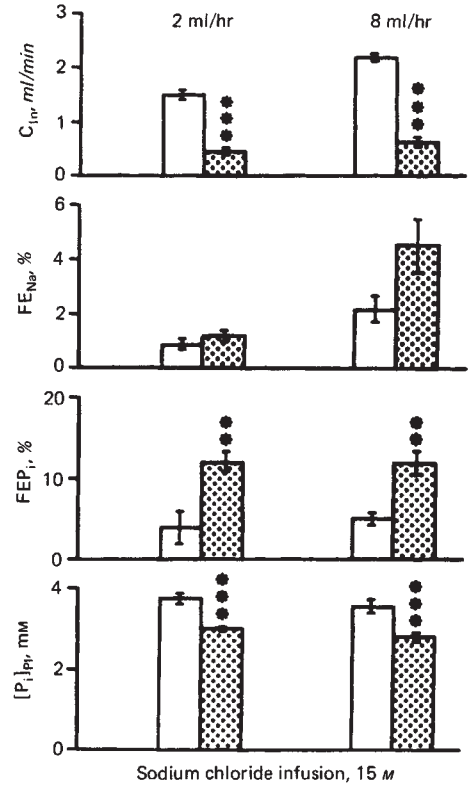

Fig. 3. *Influence of subtotal nephrectomy (NX) on the renal handling of P_i in thyroparathyroidectomized (TPTX) rats infused with an isotonic saline solution at slow and rapid rates.* Animals were thyroparathyroidectomized 50 days before the clearance study and pair-fed as in the experiment presented in Table 1. Values represent the mean ± SEM. The symbols and abbreviations used are explained: □, TPTX-control (N = 5); ⊡, TPTX-NX (N = 7); C_{IN}, clearance of inulin; FE_{NA}, fractional excretion of sodium; FEP_i, fractional excretion of phosphate; $[P_i]_{PI}$, phosphatemia; two *asterisks*, $P < 0.01$, and three *asterisks*, $P < 0.001$ compared with the respective control group. The mean (± SEM) body wt of the animals was 254 ± 3 and 244 ± 2 in TPTX-control and TPTX-NX rats respectively.

rats after subtotal nephrectomy. Indeed, avoidance of acute ECVE, or conversely, amplification of this maneuver by varying the rate of isotonic saline infusion did not influence the difference in the renal handling of P_i detectable between TPTX rats with intact and reduced renal mass.

Thus, our study in rats shows that a mechanism other than PTH is capable of altering the relationship between the total amount of P_i filtered and reabsorbed in response to renal mass reduction. A preliminary report suggests that this is also the case in dogs [23]. To what extent this change in the renal handling of P_i is a mere tubular phenomenon is not yet clear. Indeed, the increase in the filtered load of P_i per nephron [5] might contribute to this apparent tubular adaptation. Nonetheless, assuming that the alteration of the renal handling of P_i in response to the nephron loss is mainly a tubular phenomenon, the question arises: To what extent is the change observed in animals or humans with intact parathyroid glands actually due to PTH? It has been proposed [3] that PTH plays the principal role in the progressive increase in FEP_i as renal disease advances. Our results strongly suggest that this alteration could also be under the control of a PTH-independent mechanism.

Over the last five years, evidence has accumulated indicating that a factor other than PTH plays an essential role in the regulation of the net tubular reabsorption of P_i. Thus, in the absence of PTH, the renal tubule is perfectly able to adapt its P_i transport capacity in response to variation in the P_i supply [14, 15] and requirement [16–18]. Furthermore, the tubular phosphaturic action of PTH appears to be tightly controlled by this adaptation mechanism [17, 24, 25]. Therefore, it is possible that the same adaptation mechanism may contribute to the change in the renal handling of P_i observed in the course of progressive renal failure.

In a very recent study Brazy et al [26] reported that the reabsorptive P_i transport capacity of proximal convoluted tubules isolated from rabbit kidneys is not diminished after unilateral nephrectomy. This finding suggests that the mechanism of adaptation to nephron loss differs from that mechanism responding to variations in the P_i supply. However, it remains to be established whether or not a more extensive reduction in renal mass would result in a change in the P_i reabsorptive capacity similar to that observed after raising dietary P_i [26].

The present investigation also indicates that chronic PTH deficiency increases maximal TRP_i/ml GF[1] in subtotally nephrectomized rats to the same extent as in animals with a normal renal mass (Fig. 1). This finding does not favor the view that in chronic renal failure the influence of PTH on the tubular P_i transport system would be more pronounced than in a normal condition. Previous studies concerning the tubular adaptation to dietary P_i have shown also that chronic PTH deficiency increases maximal TRP_i/ml GF in rats fed either a low or high P_i diet. However, similar to the case of renal mass reduction, chronic PTH deficiency does not attenuate the decrease in maximal TRP_i/ml GF which occurs in response to a high P_i supply [19, 27].

In subtotally nephrectomized animals the elevation of FEP_i with increasing plasma P_i during acute P_i infusion was reduced (Fig. 1). This decrease was observed in TPTX as well as in SHAM rats and was related directly to the fact that acute P_i loading did not lead to a decrease in TRP_i/ml GF in subtotally nephrectomized animals as it did in those with a normal renal mass [28, 29, and our present study]. The decrease in P_i reabsorption in response to acute P_i loading in TPTX animals has been ascribed [30] to the fall in plasma calcium which usually accompanies P_i infusion [29, 30]. As is shown in Table 1, the drop in plasma calcium was, if anything, greater in the subtotally nephrectomized animals than in the ones with intact renal mass. Therefore, plasma calcium does not appear to account for the different response to acute P_i-loading observed between intact and subtotally nephrectomized SHAM or TPTX rats.

In summary, conclusive evidence has been obtained that in the absence of PTH a marked decrease in the maximal tubular P_i reabsorption per volume of glomerular filtrate can occur in chronic renal failure.

[1] Note that the difference in maximal TRP_i/ml GF between TPTX and SHAM rats can be completely abolished by the administration of small (26 pmoles/day i.p.) doses of 1,25-dihydroxyvitamin D_3. This effect of 1,25-dihydroxyvitamin D_3 can be observed in the presence of a normal renal mass [19] as well as in subtotally nephrectomized rats (Caverzasio, Gloor, Fleisch, and Bonjour, unpublished data).

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Reprint requests to Dr. J.-P. Bonjour, Department of Pathophysiology, University of Berne, Murtenstrasse 35, 3010 Berne, Switzerland

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