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Urinary excretion of prostaglandins and electrolytes in developing children

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Urinary excretion of prostaglandins and electrolytes in developing children. A longitudinal study of the urinary excretion of prostaglandins (PG's) E and F_α was performed in 55 healthy children aged from 1 to 114 months. In addition, the urinary PG's and electrolytes were studied in 6 children with Bartter's syndrome before and after an oral treatment with indomethacin. In normal children, both urinary PGE and PGF_α increased with age, more markedly before 24 months of age. During this period, a positive and significant correlation was found with the urinary osmolality ($r = 0.61$, $N = 16$, $P < 0.05$ for PGE; $r = 0.82$, $N = 16$, $P < 0.001$ for PGF_α). At every age, the urinary PG's were related to the potassium excretion ($r = 0.68$, $N = 55$, $P < 0.001$ for PGE; $r = 0.65$, $N = 55$, $P < 0.001$ for PGF_α) but not to the natriuresis. In children with Bartter's syndrome, the increased urinary excretion of PGE, PGF_α and potassium was found to be consistently reduced after indomethacin treatment when the natriuresis was either decreased or increased after treatment. These results suggest that the renal PG's might play a role in the control of potassium excretion by the kidney. In addition, the determination of normal values in different age groups appears necessary for an accurate interpretation of the urinary PG's.

Excrétion des prostaglandines urinaires et des électrolytes au cours du développement de l'enfant. L'élimination urinaire des prostaglandines (PG's) E et F_α a été étudiée chez 55 enfants normaux âgés de 1 à 114 mois ainsi que chez 6 enfants présentant un syndrome de Bartter, avant et après traitement par l'indométacine. Chez l'enfant normal, l'excrétion urinaire des PGE et PGF_α augmente progressivement avec l'âge, surtout durant les 24 premiers mois de la vie où elle apparaît significativement corrélée à l'osmolalité urinaire ($r = 0{,}61$, $N = 16$, $P < 0.05$ pour PGE; $r = 0.82$, $N = 16$, $P < 0.001$ pour PGF_α). Chez l'ensemble des 55 enfants normaux, elle n'apparaît pas liée à la natriurèse alors qu'elle est significativement corrélée à la kaliurèse ($r = 0.68$, $N = 55$, $P < 0.001$ pour PGE; $r = 0.65$, $N = 55$, $P < 0.001$ pour PGF_α). Chez les enfants présentant un syndrome de Bartter, l'élimination urinaire des PGE et PGF_α ainsi que la kaliurèse diminuent toujours sous indométacine alors que la natriurèse est soit diminuée, soit augmentée. Ces résultats suggèrent que les PG's rénales pourraient participer au contrôle de l'excrétion du potassium par le rein. Par ailleurs, il apparaît indispensable de se référer à des valeurs normales déterminées chez des sujets correctement appariés quant à l'âge pour pouvoir interpréter d'une manière correcte les dosages urinaires.

The ability of exogenous prostaglandins (PG's) to increase renal blood flow, diuresis, and natriuresis has been demonstrated during infusion studies in man and in animals [1–4]. But the relationships between the endogenous renal PG's and the urinary excretion of electrolytes remain to be defined in physiologic conditions.

It thus appeared interesting to study the relationships between the renal PG's and the urinary electrolytes at different stages of the maturation of renal function. Therefore, we followed, in normal developing children, the urinary elimination of electrolytes and of PG's, this latter having been shown to be closely related to their renal synthesis [5, 6].

Methods

Fifty-five normal children of both sexes (23 females and 32 males) aged from 1 to 114 months were included in the present study. Those aged less than 24 months were referred to the pediatric unit for benign diseases, and were considered healthy at the time of the experiment. Older children stayed with their families. All subjects studied were free of any drugs and received a standard unrestricted diet. In addition, 6 children aged from 49 to 136 months with Bartter's syndrome were studied before and 1 week after an oral treatment with indomethacin (2.4 to 3.7 mg/kg/day). Urine samples were collected for 24-hour periods. So as to minimize the endogenous release of PG's by the cells contained in the urine samples, each miction was immediately cooled to +4° C. After mixing, aliquots of the whole diuresis were obtained and stored at −20° C until the assay. These samples were analyzed for their sodium and potassium content (IL flame photometer model 143) and their osmolality (Fiske osmometer). The urinary concentrations of PGE and PGF_α were determined by our previously described radioimmunoassay [7].

Briefly, in this technique, the urinary PG's were extracted by cyclohexane and ethylacetate (1:1 vol/vol). After absorption on silicic acid columns the PGA, PGE, and PGF_α were serially eluted by solvents containing increasing concentrations of methanol in benzene and ethylacetate. Prior to the radioimmunoassay, the eluted PG's were dried under nitrogen and redissolved in phosphate buffer saline. The antibodies that we have raised could not distinguish between PG's of the series 1 or 2, but were found to be highly specific to other PG's and metabolites.

The results are expressed as the means ± SEM, and further statistical analysis used the Student's t test for unpaired data.

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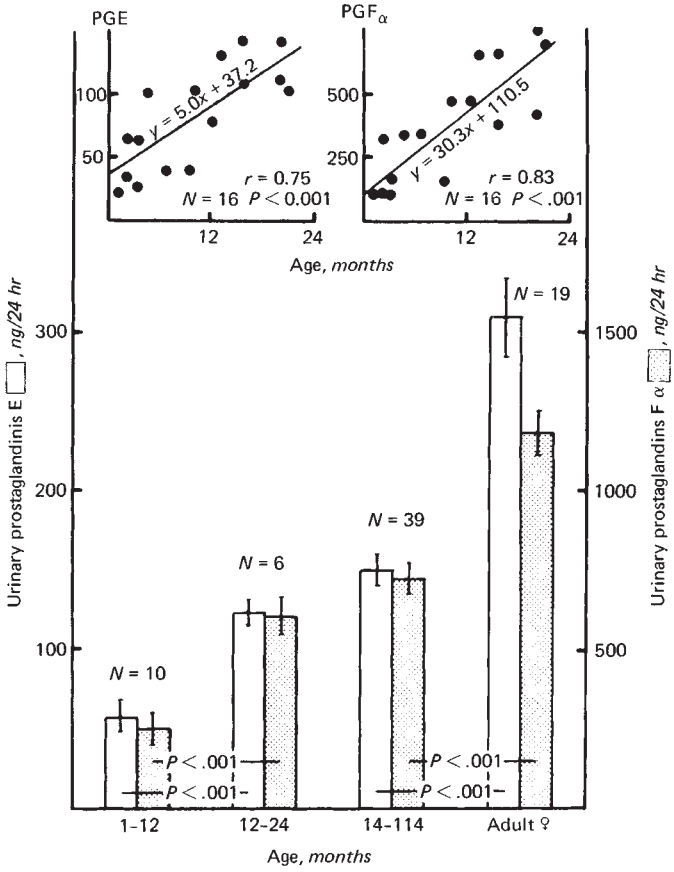

Fig. 1. *Evolution of the daily elimination of urinary PGE* (left panel) *and PGF$_\alpha$* (right panel) *in 55 healthy children aged from 1 to 114 months and in 19 normal adult women.* **Inset:** The scale has been expanded to show that both PGE and PGF$_\alpha$ are significantly related with age during the first 24 months of life.

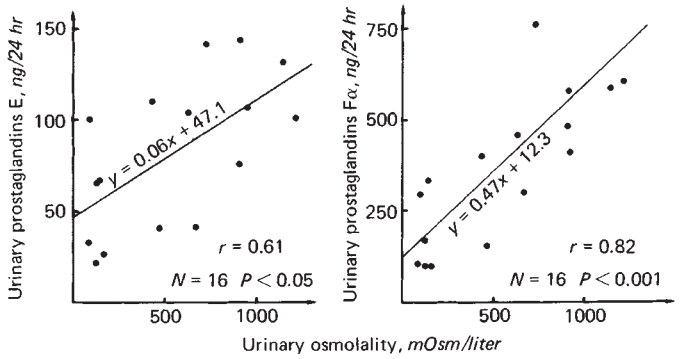

Fig. 2. *Relationship between the daily urinary excretion of PGE* (left panel), *PGF$_\alpha$* (right panel), *and the urine osmolality in 16 healthy children aged from 1 to 24 months.*

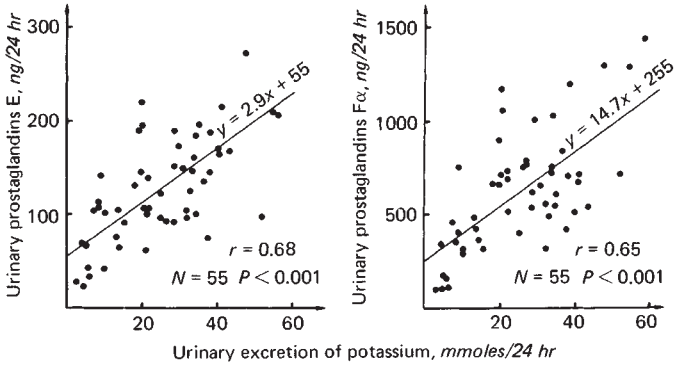

Fig. 3. *Relationship between the daily urinary excretion of PGE* (left panel), *PGF$_\alpha$* (right panel), *and potassium in 55 normal children aged from 1 to 114 months.*

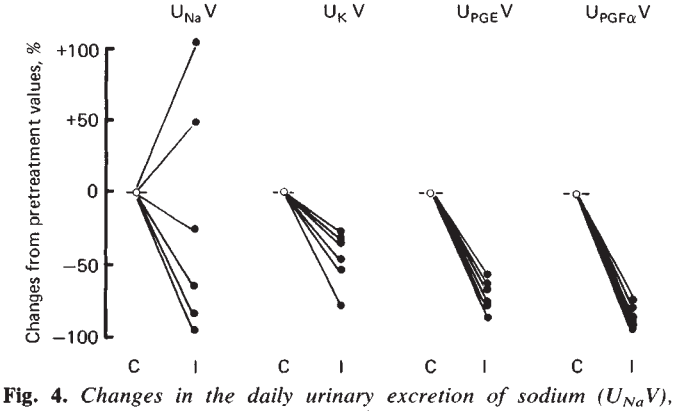

Fig. 4. *Changes in the daily urinary excretion of sodium ($U_{Na}V$), potassium (U_KV), PGE ($U_{PGE}V$), and PGF$_\alpha$ ($U_{PGF_\alpha}V$) induced by an oral treatment with indomethacin in 6 subjects with Bartter's syndrome.* The changes induced by indomethacin (I) are expressed as percentage of the pretreatment control (C) values.

Results

As no sex-related differences could be observed in developing children, the mean values were calculated from both males and females. As shown in Fig. 1, the urinary excretion of PGE and PGF$_\alpha$ increased from 1 to 114 months of age. This increase was more marked before 24 months of age, and, during this period, a positive and significant correlation with age was found for the urinary excretion of PGE and PGF$_\alpha$. In children older than 24 months, the urinary excretion of both PG's exhibited a slight increase with age but remained significantly lower than those found in adult females. The PGF$_\alpha$/PGE ratio did not change with age and was not significantly different from that observed in adult females. Still, before 24 months of age, the urinary PGE and PGF$_\alpha$ were also positively related to the urine osmolality (see Fig. 2).

From 1 to 114 months of age, the daily urinary excretion of sodium and potassium increased and was found to be significantly related with age ($r = 0.78$, $N = 55$, $P < 0.001$ for sodium; $r = 0.79$, $N = 55$, $P < 0.001$ for potassium). In addition, the urinary PG's were significantly related to the potassium excretion (see Fig. 3) but not to the sodium elimination.

Finally, as shown in Fig. 4, indomethacin treatment in 6 children with Bartter's syndrome induced variable changes in the urinary excretion of sodium. On the contrary, urinary potassium, PGE, and PGF$_\alpha$ were consistently and significantly reduced by the treatment.

Discussion

Taken as a whole, the values reported here for the urinary excretion of PG's in normal chidren are close to those previously reported by Dray [8] and Brouhard et al [9] and slightly lower

than those obtained by Haluska et al [10], a result that suggests that the method used is valuable.

Expressed as nanograms per 24 hours, both PG's appear to increase with age, more markedly during the two first years of life, which are known to be precisely a period of differentiation of the kidney [11]. Whether this steep increase of urinary PG's is related to a progressive decrease of the PG degradation associated with a stable biosynthesis as in the maturing rat kidney [12] or only to an increase of the biosynthesis could not be determined. During this same period of time, the increase of the urinary excretion of PG's was related to the increase of the urine osmolality. But, as this latter was also significantly correlated with age ($r = 0.79$, $N = 16$, $P < 0.001$), the relationship between the urinary PG's and osmolality could either be coincidental or reflect a simultaneous development of both water reabsorption capacity and PG synthesis.

In children aged from 1 to 114 months, the urinary PG's were not related with the sodium excretion, a finding that is in agreement with that of Scherer and Weber [13] but argues against the natriuretic activity exhibited by PG's when they are infused into the renal artery [1, 14]. On the contrary, the urinary excretion of PGE, PGF_{α}, and potassium was significantly related. Such a relationship, which confirms the results of Scherer and Weber [13], could not be attributed to coincidental changes in the PG synthesis and electrolyte content of the diet because, in developing children, both sodium and potassium excretion increased with age and there was no relationship between the urinary excretions of sodium and PG's. In addition, the correlation found between urinary potassium and PG's could not be due to the age factor only, as the urinary PG's were age related during the first 24 months of life but the potassium excretion was related with age up to 114 months.

Finally, the importance of the relationship found between the renal potassium handling and PG synthesis was strengthened by the demonstration that, in Bartter's Syndrome, only these two parameters were found to be significantly lowered by indomethacin treatment, which did not consistently affect the sodium excretion.

Conclusions. Two conclusions can be drawn from this study. *(1)* During development, the urinary excretions of potassium and of PG's are significantly related. Such a finding would suggest that the renal synthesis of PG's might play a role in the control of the urinary excretion of potassium, which could be of importance in the pathophysiology of Bartter's syndrome. Of course, a direct demonstration of this hypothesis needs further investigations. *(2)* From a practical viewpoint, the urinary PG's were found to increase markedly during the first 2 years of life and before puberty. It thus appears necessary to determine normal values in different age groups for the sake of the interpretation of the data obtained in young patients.

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