Paediatric Nephrology: A Research Update

Editors: D. Boda, S. Túri

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Paediatric Nephrology: A Research Update

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Foreword

The lectures featured in this publication were delivered at the 21st Annual Meeting of the European Society of Paediatric Nephrology in Budapest. The organizers of this conference had one main aim: to include those topics which best represent the most recent advances and perspectives in paediatric nephrology, both from the theoretical and the practical aspects, and to select the most outstanding contributions to these topics.

A large proportion of the papers published here deal with the latest research results achieved in connection with vasoactive mediators, kidney function and renal diseases.

Investigations relating to the effects of prostanoids, other vasoactive hormones, and, particularly, natriuretic peptides, have opened up a completely new chapter on the pathophysiology of the kidney and the relevant clinical practice.

Results that are similarly of a determining nature as concerns both theory and practice were also reported in lectures dealing with the membrane functions of the cells and with the effects of immunological factors.

Especially noteworthy are papers which were presented in the field of neonatal nephrology, demonstrating that disturbances of kidney function are currently prominent problems in disturbances of the adaptation of neonates to extrauterine life.

Extremely valuable information was provided by the reports discussing the possibilities of the prenatal diagnosis of renal diseases, in particular through the use of ultrasound and other up-to-date techniques.

By virtue of their nature, the various international scientific conferences allow a many-faceted comparison of experience on topical questions,

whereby far-reaching conclusions can be drawn and trends for the future can be decided. In this context, it may be pointed out that certain of the papers in this publication were a direct result of inter-institutional collaboration.

The editors are particularly grateful to those authors who have provided especially revised manuscripts for this volume of the Karger series 'Contributions to Nephrology'.

Domokos Boda
Sándor Túri

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Atrial Natriuretic Peptide and Other Vasoactive Hormones in Volume Regulation[1]

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Sodium balance is very well maintained in healthy subjects with renal sodium and water excretion adjusted closely to sodium and water intake, thereby preserving a constant extracellular fluid volume. The volume of this compartment is mainly determined by the quantity of sodium. Plasma volume is determined by the total extracellular fluid volume and the partitioning of this volume between extravascular and intravascular compartments according to the Starling relationship. Volume receptors detect changes in extracellular fluid volume relative to intravascular and interstitial capacitance and various renal effector mechanisms finally modify the rate of sodium excretion by the kidneys to meet the demand of volume homeostasis [14].

Various hormones with vasoactive properties play a role as renal effector mechanisms for body fluid homeostasis. In this brief communication we summarize some aspects of atrial natriuretic peptide in natriuresis induced by volume expansion and the regulation of this peptide in children with chronic renal failure. Furthermore, the role of various vasoactive hormones in edema formation of children with nephrotic syndrome is discussed.

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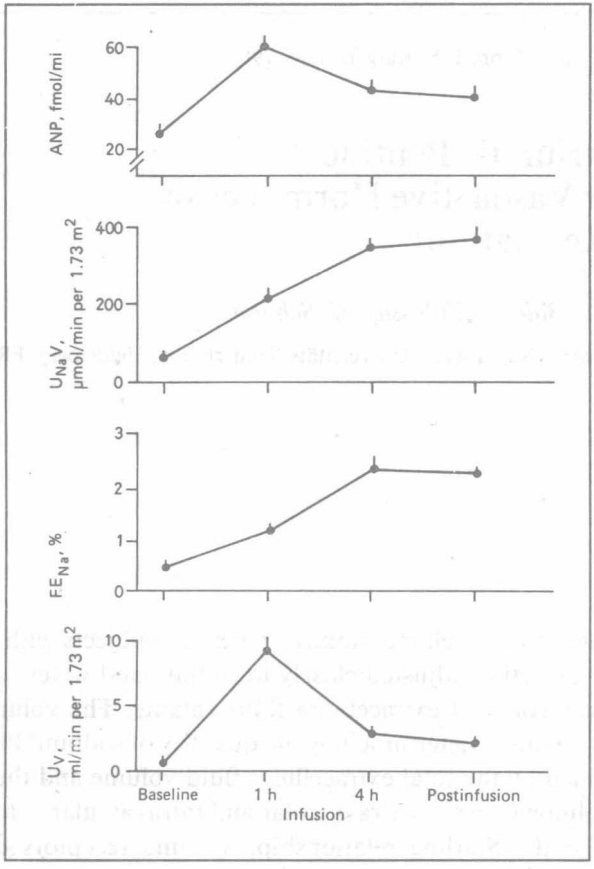

Fig. 1. Changes in plasma concentration of ANP, urinary sodium excretion ($U_{Na}V$), fractional excretion of filtered sodium (FE_{Na}), and urine flow rate (U_V) in 7 healthy volunteers following hypotonic extracellular volume expansion. Volume expansion was induced by drinking 20 ml/kg tap water and subsequent intravenous infusion of 2 liters of 0.9% saline solution over a period of 4 h.

Atrial Natriuretic Peptide and Volume Expansion

The atrial myocytes are the site of synthesis and storage of a hormone called atrial natriuretic peptide (ANP) [1, 3, 8]. It is released from cardiac atria following atrial distension [7]. Intravenous administration of human α-ANP increased urinary sodium and water excretion [12, 16].

Central volume expansion induced by saline infusion in normal volunteers [13, 18], by head-out water immersion [5] or by infusion of hyperoncotic human serum albumin solution in children with nephrotic syndrome [15], increased plasma ANP and induced natriuresis and diuresis. This indicates that expansion of the blood volume provokes the release of ANP from human atria into the circulation. ANP, in turn, promotes sodium and water excretion.

In order to study the relationship between ANP release and natriuretic response, we investigated 7 healthy, normal adult volunteers during hypotonic extracellular volume expansion (ECVE). ECVE was induced by drinking 20 ml/kg of tap water after 12 h of dehydration, followed by intravenous infusion of 2 liters of 0.9% saline over a period of 4 h. Hypotonic ECVE caused a two- to threefold increase in the plasma concentration of ANP, whereas plasma renin activity, aldosterone, vasopressin and noradrenaline levels fell. In response to ECVE, creatinine clearance rose, as did urine flow rate, urinary sodium excretion and fractional excretion of sodium (FE_{Na}) (fig. 1). There was a remarkable dissociation between the ANP response and urinary sodium excretion following ECVE. Whereas sodium excretion rose progressively over a period of 5 h, plasma ANP concentration rose threefold in the first hour of ECVE, and tended to decrease during the next 4 h. Plasma ANP appeared to be related to the diuretic response of ECVE. Thus, our results are compatible with the concept that increased ANP secretion may play a role in immediate increase in sodium excretion after hypotonic ECVE. However, they also suggest that other mechanisms may be more important for longer term natriuresis.

ANP in Children with Chronic Renal Failure

We have recently shown that children with volume overload secondary to end-stage renal disease had higher predialysis plasma concentrations of ANP than normovolemic children with advanced chronic renal failure and than normal controls [10]. Fluid removal by hemodialysis resulted in a dramatic fall of plasma ANP. This has been confirmed subsequently in adult patients [4, 6, 17].

Eight adolescents on regular intermittent hemodialysis treatment were studied during 1 h of sequential ultrafiltration followed by 3 h on hemodialysis. During removal of fluid excess by 1 h of sequential ultrafiltration plasma ANP fell from 123.8 ± 36.6 to 45.5 ± 9.3 fmol/ml ($\bar{x}$ ± SEM).

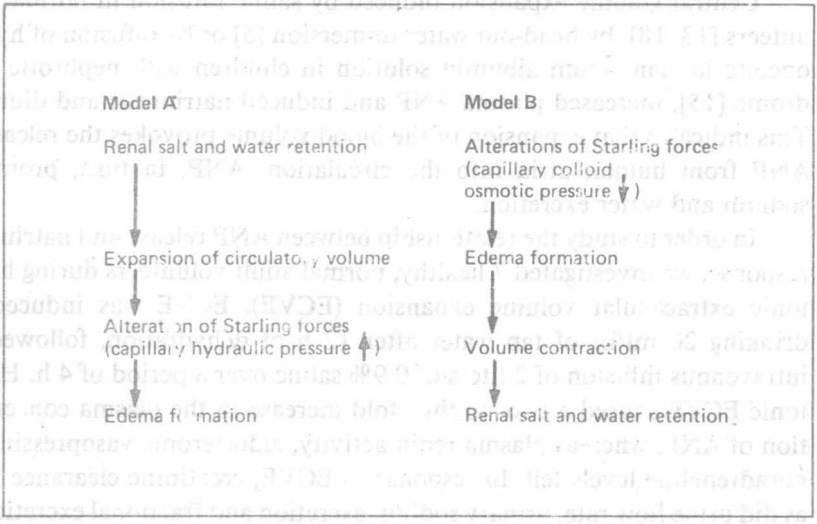

Fig. 2. Models of edema formation.

Subsequent hemodialysis combined with fluid removal for 3 h decreased ANP further down to 29.6 ± 4.6 fmol/ml. Thus, the decrease of elevated ANP during hemodialysis is mainly due to reduction of volume overload. Thus, plasma ANP appears to be a sensitive parameter for the evaluation of fluid retention in children with end-stage enal disease.

Vasoactive Hormones during Edema Formation in Children with Nephrotic Syndrome

Volume regulation is disturbed in edematous children with nephrotic syndrome. Theoretically, edema may develop by two mechanisms, i.e. when capillary hydraulic pressure increases as a result of constant elevation of plasma volume (model A) or when colloid osmotic pressure drops (model B) (fig. 2).

Neither increased capillary filtration nor decreased colloid osmotic pressure alone are sufficient to produce edema. In the presence of normal renal function a rise in capillary filtration with subsequent expansion of extracellular fluid volume results in increased natriuresis [14]. On the

other hand, low plasma colloid osmotic pressure per se does not produce edema, as demonstrated by patients with congenital analbuminemia [2]. Thus, besides capillary factors, impairment of renal sodium and water excretion contributes to edema formation. According to the classical concept of salt and water retention in patients with nephrotic syndrome reduced plasma volume should stimulate various vasoactive and volume-retaining hormone systems, which in turn promote salt and water retention. We have recently studied the role of various vasoactive hormone systems in edematous children with nephrotic syndrome [9, 11, 15]. In contrast to previous investigations in adults, we studied a homogenous group of children and adolescents suffering from steroid-sensitive nephrotic syndrome, with histologically documented minimal change disease. Patients were studied during the starting phase of edema formation, defined as an increase in body weight of more than 5% within 1 week and/or manifest edema since 3 days.

Compared to 15 healthy, age-matched children (median age 12.2 years, range 6–18 years), 17 nephrotic children (median age 11.0 years, range 2–17 years) during edema formation had higher plasma concentrations of arginine-vasopressin, noradrenaline, aldosterone and plasma renin activity [9]. Basal plasma ANP did not differ between 9 healthy controls and 9 nephrotic children. Thus, various vasoactive hormones are stimulated during edema formation and may contribute to salt and water retention.

To further evaluate the mechanism of raised hormone secretion we compared children in remission of a nephrotic syndrome to children during relapse with edema formation with respect to plasma vasopressin and water metabolism. Edematous children had marked proteinuria (5.6 ± 2.7 g/24 h per 1.73 m^2, $\bar{x} \pm$ SD), reduced serum protein and albumin concentration, and elevated serum cholesterol [9]. Serum creatinine, serum urea, serum potassium and creatinine clearance did not differ. However, serum sodium, chloride, calcium and plasma osmolality were lower and hematocrit higher in edematous children compared to children in remission [9]. The mean plasma vasopressin concentration was markedly elevated in edematous children.

Thus, vasopressin concentration is elevated during edema formation in children with nephrotic syndrome when compared either to healthy normal children or to children with nephrotic syndrome in remission. Furthermore, edematous children are slightly hypoosmolar and hyponatremic, indicating a nonosmotic stimulus for vasopressin secretion. Higher hemat-

ocrit values in proteinuric nephrotic children point to hemoconcentration and a reduced circulatory blood volume as a cause for elevated vasopressin secretion in these patients. This is corroborated by the observations of increased activity of various vasoactive hormone systems stimulated by volume reduction, such as the renin-angiotensin-aldosterone system and plasma noradrenaline.

Increase in effective circulatory blood volume should be able to suppress vasopressin secretion and release of renin, aldosterone and noradrenaline into the circulation, and consequently improve salt and water excretion. Therefore, we studied in edematous nephrotic children, the hormonal and renal responses to head-out water immersion and infusion of hyperoncotic human serum albumin solution, both procedures known to increase central blood volume.

Head-out water immersion was studied in 8 edematous children with nephrotic syndrome [11]. During 3 h of water immersion the hematocrit and serum protein concentration fell, indicating central volume expansion. Mean urine flow rose four- to fivefold as did urinary sodium excretion. Urinary potassium excretion rose threefold and osmolar clearance and creatinine clearance doubled. Plasma osmolality remained stable and urine osmolality fell. Elevated plasma concentrations of vasopressin, aldosterone, noradrenaline and plasma renin activity decreased during immersion and rose after immersion was ended [11].

Volume expansion induced by infusion of hyperoncotic serum albumin solution (20% solution, 1 g/kg per 90 min) resulted in a fall of elevated plasma concentrations of vasopressin, aldosterone, noradrenaline, and plasma renin activity. Plasma osmolality did not change. The plasma ANP concentration rose fivefold in response to albumin infusion [15]. Hyperoncotic albumin induced diuresis, natriuresis and a rise in creatinine and osmolar clearances. Urine osmolality fell, but free water clearance did not change. Changes induced by hyperoncotic albumin resembled those observed during water immersion.

Both induced central volume expansion by water immersion [11] and infusion of hyperoncotic serum albumin solution [15] reduced hematocrit values and resulted in a drop of elevated plasma levels of various vasoactive hormones to near-normal values and improved salt and water excretion.

Thus, our studies point to an important role of reduced circulating blood volume with subsequent activation of vasoactive and sodium-retaining hormones for sodium and water retention and therefore for

edema formation in children with nephrotic syndrome (according to model B from figure 2). This does not exclude that in patients with glomerular disease and nephrotic syndrome edema formation may be related to model A.

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Recent Advances in Prostanoids and Renal Disease

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Despite the involvement of many disciplines in the field of renal prostanoids, understanding of the role of prostanoids, i.e. prostaglandins and thromboxanes, in the pathophysiology of a variety of renal disease is as yet incomplete.

The range of renal disease in which disturbances in prostanoids have been implicated is shown in table I. Full discussion of each of these areas is outwith the scope of this review and the following discussion will be limited to two areas only. Firstly, that of thrombotic microangiopathy, particularly the acute childhood haemolytic uraemic syndrome (HUS), and, secondly, some aspects of prostanoids in renal transplantation. Reference will be made only to published data on prostanoids since data on leukotrienes and other arachidonic acid metabolites remain very limited and are restricted in general to experimental models.

Haemolytic Uraemic Syndrome

The ability of normal plasma to support the production of prostacyclin-like activity from vascular tissue in vitro was first reported in 1978 [1]. Subsequent attempts at characterising this activity have revealed the presence of a factor with a molecular weight of $< 10{,}000$, which apparently acts both by enhancing the release of endogenous arachidonic acid from cell membranes and by preventing self-deactivation of the vascular cyclo-oxygenase enzyme system [2].

[1] I wish to thank Mrs. Monaghan for excellent secretarial assistance.