Welcome to MEPE in the renal proximal tubule

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Maintenance of serum phosphate concentration within a narrow range is a crucial issue in mammals, given the impact of hyperphosphataemia on ageing, morbidity and all-cause mortality [1–3]. An intriguing inverse relationship between phosphataemia and lifespan has been observed through various mammalian species including man [4]. The discovery, more than a decade ago, of phosphatonin is a major event, and several peptides with the ability to inhibit renal phosphate reabsorption have been identified since [5–8].

Phosphatonin is fibroblast growth factor-23 (FGF-23) which acts on the proximal tubule in combination with Klotho to promote phosphaturia and inhibit calcitriol synthesis [5–8]. Recently, however, convincing data brought evidence for a phosphaturic effect of Klotho itself, even in the absence of FGF-23 [9].

Matrix extracellular phosphoglycoprotein (MEPE) is another protein with phosphaturic properties. Recombinant MEPE is phosphaturic and reduces serum phosphate concentrations when administered to rats in vivo [10]. The protein inhibits sodium-dependent phosphate uptake in opossum kidney cells and reduces intestinal phosphate absorption directly. MEPE also inhibits bone mineralization in vitro, and MEPE-null mice have increased bone mineralization. Infusion of MEPE reduces serum phosphate concentrations but, at variance with FGF-23, increases calcitriol concentration, a major difference which may potentially lead to renal stone formation in the case of MEPE overexpression [11,12].

MEPE expression is increased in mice with the Hyp mutation and in mice with a global knockout of the Phex gene. Although initial observations suggested that MEPE is a substrate of Phex, it appeared subsequently that MEPE is not a substrate for Phex but binds to Phex in a non-proteolytic manner, and that this interaction protects MEPE from proteolytic cleavage by cathepsin B [13–15].

In this issue of Nephrology Dialysis Transplantation [16], Shirley et al. demonstrate unequivocally that MEPE-induced phosphaturia results from inhibition of phosphate transport in the proximal tubule. Through a micropuncture study performed in rats, they show that MEPE infusion inhibited fractional phosphate reabsorption and that phosphaturia occurs in the absence of any significant change in glomerular filtration rate.

Obviously, this study is an important step in elucidating the mechanism(s) of action underlying the effects of MEPE. It opens of course a new field and raises several series of questions. The first one concerns the signalling pathways coupled to MEPE receptors. Are these receptors located in the apical or basolateral membrane of proximal tubular cells? What kind of receptor are they? What transduction pathway(s) do they trigger? Along the same line, the final target of the MEPE pathway needs to be ascertained in vivo. Although it is very likely that retrieval of NPT2a, the major renal sodium phosphate co-transporter, is the final event, isolation of brush border membranes from MEPE-treated animals will help to clarify this issue.

The second question refers to MEPE itself. Is it active in its intact form or may fragments act on renal cells? If so, where and how is MEPE processed? Recombinant MEPE as every new kid in the block, raises numerous questions and forces us to revisit and rebuild phosphate homeostasis in a more sophisticated and multidimensional manner. When the model becomes more complex, it may come closer to reality.

Conflict of interest statement. None declared.
Exposure to an adverse intrauterine environment during development predisposes offspring towards the development of hypertension in adult life [1]. We and others previously demonstrated a link between maternal undernutrition, offspring nephron complement [2–4] and blood pressure [5], supporting Brenner’s hypothesis that hypertension may be consequent to a nephron deficit [6]. In this issue of *Nephrology Dialysis Transplantation*, Osttreicher and colleagues [7] show diminished expression of 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) in the distal nephron of rats exposed to a maternal dietary protein restriction during gestation, suggesting that the elevated blood pressure observed in these animals may be the result of insufficient protection of the mineralocorticoid receptor (MR) from inappropriate binding by circulating glucocorticoids.

The enzyme 11β-HSD2 oxidizes glucocorticoids, cortisol in human and corticosterone in rodents, to form the inactive 11-ketoglucocorticoids cortisone and 11-dehydrocorticosterone, respectively. The affinity of the MR for aldosterone and glucocorticoids is similar [8]; however, glucocorticoids circulate at concentrations of up to 1000-fold that of aldosterone. In order for the MR to respond exclusively to aldosterone in specific tissues therefore, it is necessary for 11β-HSD to prevent cortisol from reabsorption. *Nephrol Dial Transplant* 2008; 23: 730–733


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Programmed repression of tubular 11β-HSD2—a novel form of AME?

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