Nephropathy) will evaluate the effect of cyclosporin A versus no immunosuppressive treatment in 186 patients with idiopathic membranous nephropathy, reduced renal function (creatinine clearance < 60 ml/min/1.73 m²) and persistent nephrotic syndrome with a follow-up of 3.5 years [14]. Participation of many centres is warmly welcomed in order to achieve the goals of these studies so that some parts of the dilemma of the treatment of idiopathic membranous nephropathy can be solved in a collaborative European effort.

References


Parathyroid-hormone-related protein: a previously unrecognized renal vasodilator

T. Massfelder¹, A. F. Stewart² and J. J. Helwig¹

¹Laboratoire de Physiologie Cellulaire Renale, CJF INSERM 94-09, Université Louis Pasteur, Strasbourg, France; and
²Division of Endocrinology, West Haven VA Medical Center, West Haven, Connecticut 06516, and Yale University School of Medicine, New Haven, CT 06520, USA

Introduction

Parathyroid-hormone-(PTH)-related protein, or PTHrP, is now widely recognized as the factor primarily responsible for the syndrome of humoral hypercalcaemia of malignancy (HHM) [1]. A key structural characteristic of PTHrP is a stretch of 13 amino acids at the amino-terminus which shares 70% homology with PTH which accounts for the ability of PTHrP to cause the clinical features of HHM. In humans, the PTHrP gene encodes three isoforms of 139, 141, and 173 amino acids resulting from alternate splicing of the immature messenger RNA transcript. In the rat and mouse, only a single mRNA species has been found. The amino acid sequence of PTHrP is highly conserved across species, suggesting that it plays a key role in normal cellular function. Indeed, since its discovery in 1987 in tumours associated with hypercalcaemia, PTHrP has been shown to be produced by a broad array of normal tissues in which it exerts both classic PTH-like as well as PTH-unlike effects.

PTHrP is initially translated as a precursor or pro-hormone which is subsequently posttranslationally cleaved into a family of daughter peptides, each of which is likely to have different physiological functions. In this way PTHrP is closely analogous to other neuroendocrine peptide hormone precursors. For example, pro-opiomelanocortin serves as the initial translation product from which ACTH, MSH, beta-endorphin, and lipotrophin are derived. In the normal tissues, which produce PTHrP, it appears to function along three thematic roles: PTHrP acts as a regulator of cellular growth, differentiation, and development; it acts as a regulator of transepithelial calcium transport; and it acts as a relaxant of smooth muscle [2].
In this regard PTHrP has been detected under normal physiological conditions in a wide variety of vascular and non-vascular smooth muscle types. It has been demonstrated to exhibit potent hypotensive, inotropic, chronotropic and smooth muscle relaxant properties by interacting with a common PTH/PTHrP receptor [3]. Interestingly, in smooth muscle, PTHrP expression is induced by physiological stimuli including cytokines, peptide hormones or mechanical stretch [4]. Thus in contrast to PTH, which is exclusively secreted by parathyroid glands and which circulates in concentrations which influence only renal tubular and skeletal physiology, PTHrP almost certainly acts in an autocrine/paracrine manner to regulate vascular tone. This brief comment focuses on the potential for PTHrP to regulate renal and glomerular blood flow.

**PTH/PTHrP receptors in the kidney vasculature**

Radioiodinated amino-terminal PTHrP and PTH bind to renal tubules and glomerular arterioles in a saturable and specific manner, with Kd values in the nanomolar range [5]. Hill coefficients were consistent with a one-site model in both tissues. The specificity of tubular and arteriolar receptors for PTH-like peptides is high: structurally unrelated peptides as calcitonin, ANF or CGRP are unable to compete with PTH or PTHrP. These receptors are coupled to the cAMP signaling pathway. PTHrP and PTH stimulate renal adenylyl cyclase with EC50 values ranging from 0.5 to 3 nM in arterioles and from 7 to 30 nM in tubules [6]. Amino-terminally truncated PTH or PTHrP fragments, which are potent PTH receptor antagonists, inhibit PTHrP-stimulated adenylyl cyclase activity in renal arterioles. The guanylyl nucleotide, GTP, markedly enhances the adenylyl cyclase responses to the peptides. Evidence for the presence of adenylyl cyclase-dependent action of PTHrP in the glomerulus has also been found, supporting the possibility that PTHrP could also affect glomerular functions by increasing intracellular cAMP content [7].

**Vasodilatory properties of PTH/PTHrP in the kidney**

**In vitro studies**

PTHrP has been shown to cause vasodilatation in the rat and rabbit kidney. In the isolated rabbit kidney, it is a potent relaxant of the preconstricted renal arterial system [9]. In the isolated rat kidney, both amino-terminal PTHrP and PTH cause prompt, transient, concentration-dependent vasodilatation that is competitively inhibited by PTH or PTHrP receptor antagonists and that is unrelated to prostaglandins or noradrenaline release [6]. Effects of PTH and PTHrP have also been investigated in afferent and efferent arterioles microdissected from rabbit kidneys. Both aminoterminal PTHrP as well as PTH markedly relax both afferent and efferent arterioles preconstricted with noradrenaline, again with EC50 values in the nanomolar range [8]. Until recently, the signalling pathways accounting for the renal vasodilatory properties of PTHrP have received little attention. Recently, however, it has been shown that the vasorelaxant response to amino-terminal PTHrP in the rabbit kidney involves a nitric oxide (NO)-synthase pathway, as evidenced by the inhibitory action of L-NAME, a competitive inhibitor of NO-synthase, on PTHrP-induced relaxation [9]. As PTHrP also stimulates cyclic AMP production in isolated renal arterioles, the question as to how cyclic AMP interacts with NO to trigger renal relaxation remains unexplored. In addition, the question as to whether PTHrP affects cytosolic calcium content in arterial smooth muscle cells will need specific investigation. It has been shown in non-renal vascular smooth muscle cells that PTH and PTHrP could act as calcium-channels blockers or as inhibitors of intracellular calcium release from internal stores [10].

**In vivo studies**

Complementing the observations described above using isolated kidney preparations, PTHrP has also been found to be a potent vasodilator in intact animals. In 1989 the in-vivo haemodynamic properties of PTHrP were elegantly described by Rocca-Cusachs et al. [11]. These authors showed that PTH and PTHrP decreased renal vascular resistance without affecting renal blood flow, events which were associated with systemic vasodilatation. The precise localization and quantitation of the vasodilatory effect of PTHrP along the intrarenal vascular tree and the potential for PTHrP to modulate glomerular blood flow and filtration rate has recently been investigated in the split hydronephrotic rat kidney model [12]. This model allows the in-situ measurement of single glomerular blood flow and of luminal diameters of each of the intrarenal vascular segments [12]. These studies demonstrate that locally applied amino-terminal PTHrP induces vasodilatation in all preglomerular arterial segments in a time- and concentration-dependent manner with effects starting at 0.01 nM and with EC50 values in the subnanomolar range. The most prominent effect is observed in the interlobular artery and in the afferent arteriole where a 35% increase in vessel diameter is observed following exposure to 100 nM PTH or PTHrP. The preglomerular vasodilatation results in a parallel increase in glomerular blood flow, reaching 60% and 70% above basal flow for 100 nM PTH and PTHrP, respectively. Interestingly, after exposure to angiotensin-converting enzyme inhibitor, PTHrP also displays a vasodilatory effect on the efferent arteriole. These results strongly suggest that, under basal conditions, postglomerular dilatation induced by PTHrP is obscured by preglomerular production of angiotensin II. As indicated in the following section, this in turn may result from PTHrP-induced renin release.

**PTHrP and renin release**

PTHrP directly stimulates renin release from juxtaglomerular secretory cells [13]. This effect has been
observed in the isolated perfused kidney and is independent of pressure-related mechanisms [13]. The renin-releasing effect of PTHrP on juxtaglomerular cells is direct, since this action is also observed in isolated glomeruli and in collagenase-dispersed cortical cells (enriched in juxtaglomerular cells) [13]. This effect is independent of prostaglandin production but is dependent on extracellular calcium [13].

**Conclusion: a potential role of PTHrP in the renovascular homeostasis**

On the basis of the findings summarized herein it seems likely that PTHrP may be involved in the regulation of renovascular homeostasis. One piece of evidence which is still missing from the puzzle is whether PTHrP is actually produced within the renovascular tree. PTHrP is well known to be produced in arterial smooth muscle in a variety of locations [2]. Preliminary immunohistochemical findings in our laboratories indicate that PTHrP is present in abundance in vascular smooth muscle cells and endothelial cells throughout the renovascular tree [Massfelder, Stewart, Helwig, unpublished observations]. In addition, immunoreactive PTHrP is present in glomeruli and tubules and its production is upregulated after ischemic injury [14]. The facts that angiotensin II and NO appear to play a role in the modulation of renal haemodynamics and that angiotensin II is able to upregulate endogenous PTHrP [4] suggest that PTHrP interacts within the regulatory renin/angiotensin/NO balance within the kidney. Clarification of these issues will undoubtedly occur in the near future.

**References**


**The kidney in essential hypertension: a Cinderella of hypertension research**

G. Maschio

Division of Nephrology, University of Verona, Italy

**Introduction**

An increasing prevalence of hypertensive nephropathy (HN) as the cause of end-stage renal failure (ESRF) is now the most regular finding in all national registries both in Europe and in USA [1]. It is quite possible that the incidence of HN is overestimated, since its diagnosis may be difficult for several reasons:

(a) hypertension is seldom the only aetiological factor;
(b) there are forms of nephrosclerosis that are not linked to hypertension;

**Correspondence and offprint requests to: Giuseppe Maschio MD, Divisione Nefrologia, Ospedale Civile Maggiore, 37126 Verona, Italy.**