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The renin-secreting cell and the glomerular peripolar cell in renal artery stenosis and Addison's disease

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Summary. The glomerular peripolar cell may be a secretory component of the juxtaglomerular apparatus. To investigate this hypothesis we studied kidneys with the renin-angiotensin system activated by two different stimuli in order to compare the responses of peripolar cells and renin-secreting cells. We examined 10 human kidneys, removed for renal artery stenosis and 11 autopsy cases of Addison's disease with appropriate controls. We counted granulated peripolar cells in serial paraffin-embedded sections and renin-containing cells were quantified using an immunoperoxidase technique with an antiserum to human renin. There was a five-fold increase in the number of renin-containing cells in both renal artery stenosis and in untreated, but not in treated, Addison's disease. Peripolar cells were increased in number in three cases of renal artery stenosis, but were unaltered in both treated and untreated Addison's disease. Therefore, neither a reduction in renal perfusion pressure (renal artery stenosis), nor sodium depletion (Addison's disease) consistently affect peripolar cells in humans. These findings do not support the hypothesis that the peripolar cell is part of the juxtaglomerular apparatus.

Key words: Peripolar cell – Renin – Juxtaglomerular apparatus – Kidney

Introduction

The glomerular peripolar cell has been described in the kidney of most species studied, including humans (Ryan et al. 1979; Gardiner and Lindop 1985; Gall et al. 1986). These cells occupy a unique site in the glomerulus where they form a cuff around the vascular pole interposed between the visceral and parietal epithelial cells within Bowman's capsule (Ryan et al. 1979; Gardiner and Lindop 1985). Peripolar cells contain multiple, intra-cytoplasmic granules, which undergo exocytosis into the urinary space (Hanner and Ryan 1980; Hill et al. 1983), suggesting a secretory function (Ryan et al. 1979). The granules contain plasma proteins, but the function of the cell remains uncertain (Trahair and Ryan 1988; Gardiner and Lindop 1992). The position of the peripolar cell at the vascular pole of the glomerulus raises the possibility of interaction with the juxtaglomerular apparatus (JGA); indeed it has been suggested that the peripolar cell could be an additional secretory component (Ryan et al. 1979; Gardiner and Lindop 1985; Turner 1985). To investigate this relationship, we have studied peripolar cells and renin-containing cells (RCCs) in renal artery stenosis, and in Addison's disease. In both diseases there is stimulation of the renin-angiotensin system, but by different mechanisms.

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Materials and methods

We examined 10 cases of renal artery stenosis and 11 cases of Addison's disease together with control cases for each group.

In the renal artery stenosis group, the nephrectomies were performed to relieve renovascular hypertension. The files of the Department of Pathology, Western Infirmary were searched for all cases in which suitable blocks were available. Control cases were surgically removed kidneys from age- and sex-matched patients which were histologically normal: 4 were removed because of renal stones, 3 were removed following trauma and 1 each for unexplained haematuria and chronic loin pain.

Data regarding patients who died during addisonian crisis were obtained by searching death certificates of England and Wales for the past 20 years. Autopsy reports and tissue blocks were obtained from the pathologists concerned. In 5 patients, fatal crisis was the initial presentation of Addison's disease, whilst 1 patient had shown poor compliance with treatment. We also examined 5 other cases of Addison's disease treated long term with corticosteroids, but who died in crisis shortly after adminission to hospital. Eleven age- and sex-matched kidneys from medico-legal autopsies performed for sudden deaths were used as controls.

All kidneys had been formalin-fixed, embedded in paraffin wax and processed routinely for diagnostic histology. We selected only blocks which included the full width of the renal cortex, and examined areas which avoided medullary rays and columns of Bertin.

Fifty serial 3 μm sections were cut and stained by Lendrum's Martius-Scarlet Blue technique (Lendrum et al. 1962). We counted

peripolar cells by following the vascular poles of individual glomeruli through the serial sections. We studied 20–25 glomeruli from all levels of the renal cortex. The number of glomeruli with at least one granulated peripolar cell was expressed as a percentage of the total number of glomeruli examined – the peripolar cell index (PPI) (Morild et al. 1988; Gardiner et al. 1985).

We then mapped the position of each glomerulus with a peripolar cell within the renal cortex as before (Gardiner and Lindop 1985; Graham et al. 1990; Kelly et al. 1990), measuring the distance, in high power fields, between the cortico-medullary junction and the glomerulus, and then the distance between the cortico-medullary junction and the kidney surface in the same straight line. The ratio of the two measurements represents the relative position within the renal cortex; this was plotted on a scatter diagram.

Immunohistochemistry. The first and last of the serial sections were mounted on polylysine-coated slides and stained by an immunohistochemical technique using an antiserum to pure human renin as previously described (Lindop et al. 1987; Graham et al. 1990).

RCCs were quantified using an established technique (Nochy et al. 1983; Gardiner and Lindop 1985):

$$\text{JGA}+ = \frac{\text{Number of glomeruli with renin-containing JGAs}}{\text{Number of glomeruli}} \times 100$$

$$\text{JGA}++ = \frac{\text{Number of JGAs with more than 6 RCCs}}{\text{Total number of renin-containing JGAs}} \times 100$$

$$\text{A}+ = \frac{\text{Number of arterial sections with RCCs}}{\text{Number of glomeruli}} \times 100$$

In addition we devised a renin-cell index (RCI):

$$\text{RCI} = \frac{\text{Total number of RCCs}}{\text{Number of glomeruli}} \times 100$$

We examined at least 100 glomeruli in all layers of the renal cortex in two sections of kidney from each case.

No clinical data were available for the Addison's patients. The following pre-operative data were noted for each renal artery stenosis patient: systolic and diastolic blood pressure, haemoglobin, and plasma levels of sodium, potassium, urea and creatinine, and also in the majority, creatinine clearance, quantitative proteinuria, plasma renin, angiotensin II and aldosterone concentrations.

Statistical analysis. The Mann-Whitney U-test was used to examine differences between means, and Spearman's rank correlation coefficient was used to assess the relationship between variables.

Results

The renal artery stenosis group showed tubular atrophy with glomerular crowding and tuft contraction. In both treated and untreated Addison's disease the kidneys were normal but the adrenals were atrophied and showed histological evidence of autoimmune adrenalitis.

In both control groups RCCs were present in the afferent glomerular arterioles and were occasionally identified in the efferent arterioles and in interlobular arteries.

In the renal artery stenosis kidneys there was hyperplasia of RCCs with frequent extension into the glomerular arterioles and interlobular arteries (Fig. 1). Compared to the normal kidneys the renin indices were markedly elevated (JGA+, $P<0.002$; JGA++, $P<0.02$; RCI, $P<0.002$) (Table 1). The arterial index (A+) was also elevated but this did not achieve statistical significance. There was no correlation between PPI and the renin indices.

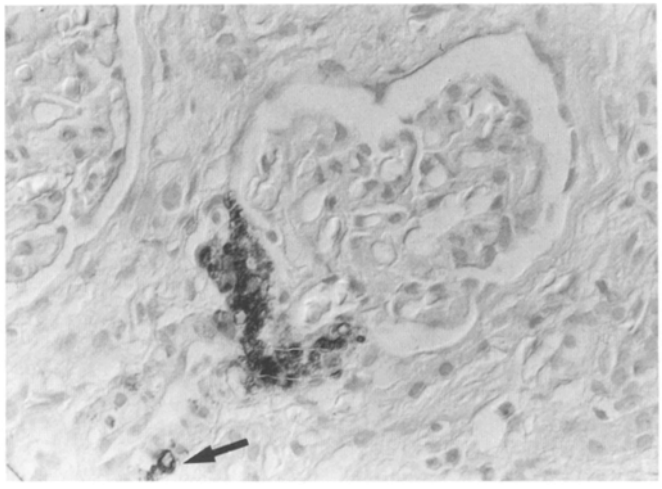

Fig. 1. Hyperplasia of the renin-containing cells in renal artery stenosis. Note the cells in the proximal afferent arteriole (*arrow*). PAP technique, interference contrast microscopy ×350

Table 1. Mean renin indices (±SEM) for each group – see text for definitions of indices

(a) Renal artery stenosis

Renin index	Controls	Renal artery stenosis	
JGA+	11.6 (±1.7)	39.2 (±2.4)	$P<0.002$
JGA++	15.4 (±7)	43.6 (±7)	$P<0.002$
A+	1.6 (±0.5)	5.4 (±1.6)	NS
RCI	32.9 (±6.4)	170 (±28)	$P<0.002$

(b) Untreated Addison's disease

Renin index	Controls	Addison's disease	
JGA^+	8.8 (±2.5)	30.2 (±4.2)	$P<0.002$
JGA^{++}	9.5 (±2.2)	38.5 (±9.0)	$P<0.001$
A^+	1.9 (±0.4)	5.8 (±1.49)	$P<0.013$
RCI	32.4 (±8.4)	160.4 (±24.8)	$P<0.001$

(c) Treated Addison's disease

Renin index	Controls	Addison's disease	
JGA^+	10.0 (±3.3)	9.7 (±5.8)	NS
JGA^{++}	5.2 (±2.4)	11.4 (±5.2)	NS
A^+	2.7 (±1.3)	2.5 (±1.3)	NS
RCI	37.9 (±12.1)	66.5 (±35.2)	NS

In untreated Addison's disease there was striking hyperplasia of the RCCs in the JGA, and in the walls of glomerular arterioles and interlobular arteries (Figs. 2, 3). All renin indices were significantly elevated (JGA+, $P<0.002$; JGA++, $P<0.001$; A+, $P<0.013$; RCI, $P<0.001$) (Table 1).

Kidneys from patients with treated Addison's disease contained normal numbers of RCCs and there was no difference in the renin-indices between these patients and age-/sex-matched controls (Table 1).

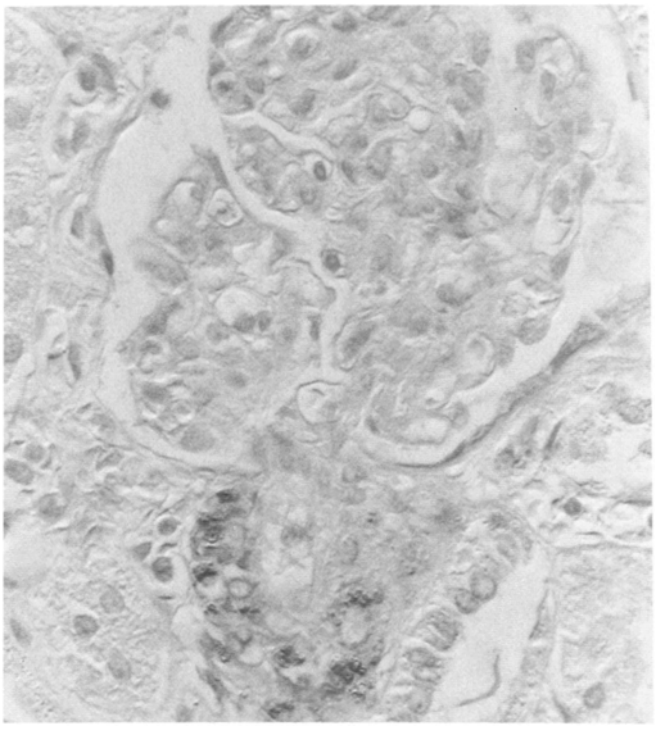

Fig. 2. Hyperplasia of the renin-containing cells in the juxtaglomerular apparatus in Addison's disease. PAP technique, interference contrast microscopy ×700

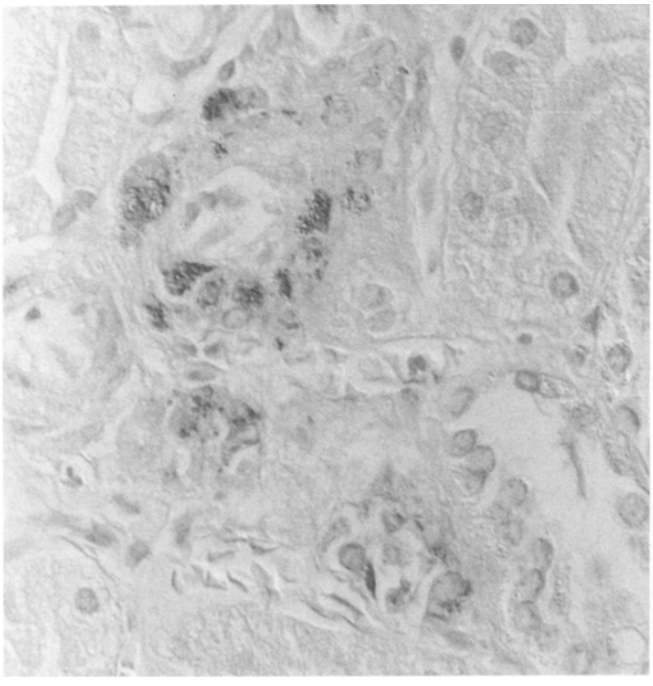

Fig. 3. Renin-containing cells in the proximal afferent arteriole in Addison's disease. PAP technique, interference contrast microscopy ×600

Table 2. Mean peripolar cell index (PPI) (±SEM) for each group

	PPI
Renal artery stenosis	16.2 (±6.8)
Controls	7.6 (±2.4)
Untreated Addison's disease	3.0 (±2.2)
Controls	0.72 (±0.72)
Treated Addison's disease	4.0 (±2.4)
Controls	1.9 (±1.2)

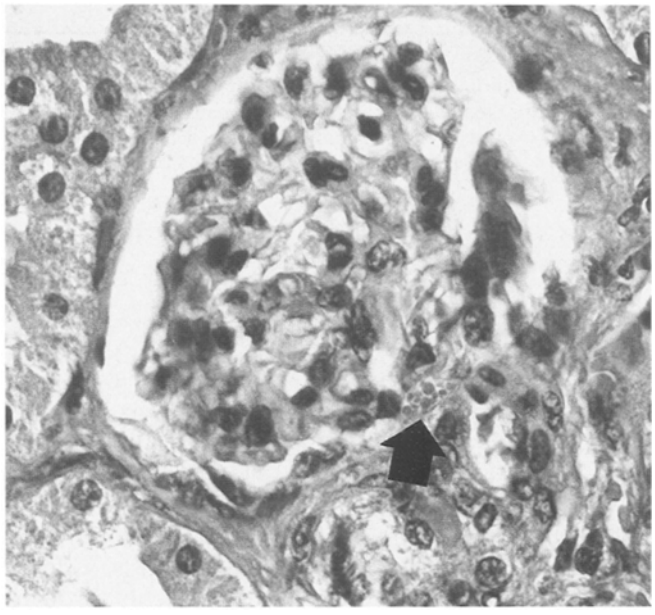

Fig. 4. A peripolar cell (*arrow*) at the vascular pole in renal artery stenosis. Note the cytoplasmic granules. MSB trichrome stain ×450

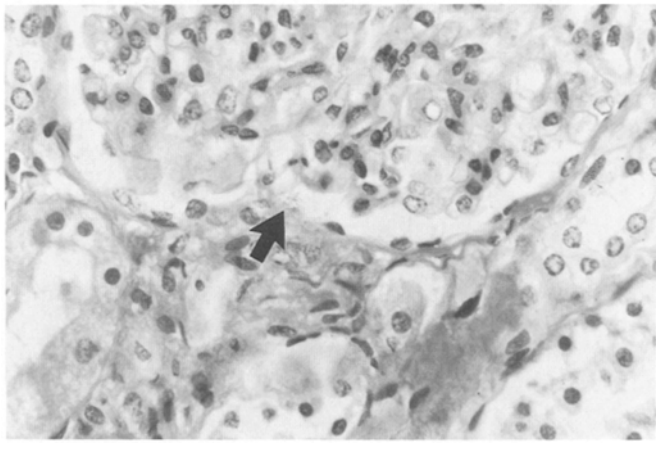

Fig. 5. A peripolar cell (*arrow*) at the vascular pole in Addison's disease. MSB trichrome stain ×700

Granulated peripolar cells were identified in 6 of the 9 normal kidneys (Table 2). The PPI varied between 0 and 21 (mean = 7.6). Peripolar cells were present in 7 out of the 10 cases of renal artery stenosis (Fig. 4, Table 2). The PPI ranged between 0 and 64 [mean (SEM) = 16.2 (6.8)]. There was no significant difference in PPI between the two groups, nor were there any differences in peripolar cell morphology or degree of granulation.

In untreated Addison's disease peripolar cells were present in only 2 out of the 6 kidneys (Table 2, Fig. 5)

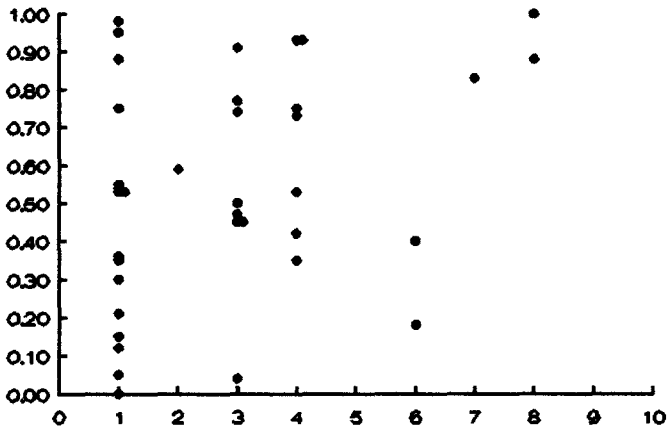

Fig. 6. Distribution of peripolar cells in the renal cortex in renal artery stenosis. Generally peripolar cells are confined to the superficial cortex; however, case 1 contains numerous peripolar cells, which are evenly distributed. See text for method of plotting

(PPI 4.5 and 13.6). The difference between this and the mean PPI of their controls (0.72) was not statistically significant.

In treated Addison's disease peripolar cells were present in 2 out of the 5 kidneys (PPI = 10.0 for both) and the mean PPI was 4.0 (Table 2). The mean PPI of the control group (1.9) was not significantly different and there was no difference between treated and untreated patients. There was no correlation between PPI and any of the renin indices in any of the groups.

The distribution of glomeruli with peripolar cells was mapped only for the renal artery stenosis kidneys (Fig. 6); the peripolar cells were spread evenly throughout the renal cortex. There were too few peripolar cells in the other kidneys and in Addison's disease to produce meaningful plots.

PPI only correlated with diastolic blood pressure for normal nephrectomies ($P<0.05$) but not for the cases of renal artery stenosis. PPI did not correlate with other clinical parameters or drug therapy. There was no relationship between the renin indices and the clinical data, including plasma renin activity and blood pressure.

Discussion

We have confirmed early reports of hyperplasia of the JGA in renal artery stenosis (Tobian et al. 1958; Turgeon and Sommers 1961; Brown et al. 1964) and later immunohistochemical studies of RCCs in human (Camilleri et al. 1980; Farragiana et al. 1982; Graham et al. 1990) and experimental renovascular hypertension (Taugner et al. 1981; Cantin et al. 1984).

Addison's disease results in deficiency of adrenocortical hormones (Anderson 1985); the lack of aldosterone leads to sodium depletion and hyponatraemia. Consequently, these patients have high plasma renin levels which return to normal after treatment (Brown et al. 1964). There have been previous reports of JGA hyperplasia in Addison's disease (Alexander 1968; Christensen et al. 1976), but this is the first immunohistochemical study of RCCs. All semi-quantitative indices of RCCs were elevated. The values were similar to those in renal artery stenosis (about five times normal); in both cases the RCCs may be maximally stimulated. In contrast, in treated Addison's disease, the RCC numbers were normal, even in crisis. Hence treatment with salt and steroids was sufficient to restore RCC content to normal.

Peripolar cells have been recognised in many species (Gall et al. 1986). We have confirmed that granulated peripolar cells are sparse in normal human kidneys. The PPI was similar to our previous study of normal human kidneys (Gardiner and Lindop 1985).

The purpose of this study was to investigate the reactions of the human peripolar cell in sodium depletion and a reduction in renal perfusion pressure, the main stimuli to the JGA. Three kidneys with renal artery stenosis contained large numbers of peripolar cells, more than twice any of the normal kidneys, although as a group there was no significant difference; no clinical or pathological features characterised these patients. We have shown an even distribution of peripolar cells in the renal cortex in renal artery stenosis, but there were too few cells in the normal kidneys to assess their distribution. It has previously been been suggested that peripolar cells are more prominent in superficial cortical glomeruli (Gardiner and Lindop 1985; Gall et al. 1986; Gibson et al. 1989); however this may be due to the relative numbers of glomeruli in different zones of the kidney (Kelly et al. 1990).

Peripolar cells were sparse in both groups of Addison's patients and in the control groups. The mean PPIs of the autopsy control groups were lower than the normal nephrectomy control kidneys in the renal artery stenosis study. The reason for this is uncertain but peripolar cells may be more difficult to identify in autopsy kidneys. There was no difference in PPI between the treated and untreated groups of Addison's disease. Glomerular epithelial cells become granulated in normal fetal kidneys, and this may be prevented by maternal adrenalectomy (Dhiab al Naimy and Bearn 1981). In our study neither sodium depletion nor adrenal cortical deficiency affected peripolar cells in humans.

The morphology of the peripolar cell has been well studied, but there are few clues to its function. Its granules are secreted by exocytosis into the urinary space of Bowman's capsule (Hanner and Ryan 1980; Hill et al. 1983) and it has been suggested that the secretory product may influence tubular function. Acute sodium depletion in sheep (Hill et al. 1983) and chickens (Morild et al. 1988) increases the numbers of granulated peripolar cells. Peripolar cells do not contain renin (Gardiner and Lindop 1985; Morild et al. 1988; Trahair et al. 1989). Urinary kallikrein secretion is increased in human and experimental renovascular hypertension (Scicli and Carretero 1986) but whether or not kallikrein is present in sheep peripolar cells is controversial (Xiong et al. 1989; Trahair et al. 1989). Renal kallikrein mRNA has been localised to the vascular pole of rat glomeruli, but not specificially identified in peripolar cells (Xiong et al. 1989).

Other plasma proteins are present in peripolar cells (Nakajima et al. 1989; Trahair and Ryan 1988; Gardiner

and Lindop 1991). Some have suggested that peripolar cell granules are lysosomal in nature and represent non-specific resorption of protein from the glomerular filtrate (Morild et al. 1988; Trahair et al. 1989); the evidence is reviewed in (Gardiner et al. 1991). Proteinuria occurs in both benign (Parving et al. 1974) and malignant hypertension (Kincaid-Smith et al. 1958) and in renovascular hypertension (Berlyne et al. 1964; Montolin et al. 1979). Protein reabsorption droplets are present in other glomerular epithelial cells in the unclipped kidney of Goldblatt hypertension in rats (Szokol et al. 1979). However, in this study, we found no granulated glomerular cells other than peripolar cells, and the amount of urinary protein did not correlate with numbers of peripolar cells.

In summary, there was a five-fold increase in RCCs both in renal artery stenosis and in untreated (but not in treated) Addison's disease. Peripolar cells were not significantly altered in either condition, suggesting that they are not part of the JGA.

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