Glomerular hyperfiltration and hypertrophy in the rat hypoplastic kidney as a model of oligomeganephronic disease

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Abstract

Background. Rat male hypogonadisim (hgn/hgn) is accompanied by bilateral hypoplastic kidney (HPK). The HPK contains a reduced number of nephrons that progress to chronic renal failure. In this study, we describe the renal pathophysiology in adult HPK rats as a potential model of oligomeganephronic disease.

Methods. Urine and blood samples were collected from adult male HPK rats and phenotypically normal littermates at 70 days of age for measurements of urea-nitrogen and creatinine clearances (Cun and Ccr). Glomerular number (GN) and glomerular projective area were determined using the maceration method. Blood pressure was measured. Urinary protein and renal histology were examined. Urinary albumin concentration was determined at early postnatal ages.

Results. Renal weight was significantly smaller in adult HPK males than in normal males. Polyuria and polydipsia were observed in HPK rats. Ccr and Cun were low in HPK rats compared with those in normal rats. The HPK contained only 20% of the nephrons present in normal kidneys. The Cun and Ccr divided by GN (average values of single nephron Cun and Ccr) of HPK rats were about two and four times greater than normal levels, respectively. This hyperfiltration was not accompanied by systemic hypertension, but was associated with marked glomerular hypertrophy and glomerulosclerosis, which were observed mainly in the inner cortex. A considerable heterogeneity of glomerular size was found in HPK and most glomeruli of surface nephrons retained normal size and histology. A remarkable leakage of albumin into urine was found at 35 and 70 days of age.

Conclusions. The HPK rat is a useful model for studying the pathophysiology of oligomeganephronic disease as well as glomerular hyperfiltration and hypertrophy induced by severe congenital reduction of nephrons.

Keywords: hyperfiltration; hypertrophy; oligomeganephronia; oligonephropathy; renal hypoplasia

Introduction

Kidney development is a complex process involving growth and branching of collecting ducts from the ureteric bud, as well as the induction and differentiation of nephrons from the metanephric blastema. Reduced nephrogenesis during kidney development results in renal hypoplasia [1]. Oligomeganephronia (OMN), the most common form of human congenital renal hypoplasia, is characterized by extremely enlarged nephrons and a marked decrease in their total number [2–5]. The main manifestations of early-stage OMN are polydipsia, polyuria, proteinuria and growth impairment [2,3]. Human OMN results in progressive renal failure and advances to end-stage renal failure [2–4]. Although recent studies suggest that genetic factors are involved in the occurrence of some cases of OMN [3,5,6], the aetiology of the disease remains undetermined [2,3].

A small number of hereditary murine models showing congenital reduced nephron mass have been reported [4,7,8]. These models have been used for assessing the relationship between congenital renal mass and renal disease, since it has been reported in humans that the number of nephrons varies per individual and that low nephron number is a risk factor for cardiovascular disease [3,4,8]. However, these models are not always accompanied by hypertrophied nephrons and they do not progress to renal failure in the absence of additional renal mass deletion [4,7,8]. In addition, there are no hereditary animal models that develop congenital OMN with clinical symptoms.
Rat hypoplastic kidney as a model of oligomeganephronia

similar to those of human OMN [1,4]. The mechanism through which congenital reduction of renal mass causes nephron hypertrophy is not clear [3]. Although it has been hypothesized that hyperfiltration, secondary to a congenital severe reduction in nephron mass, is detrimental to glomerular function and structure, this hypothesis has not been investigated adequately due to the lack of suitable experimental animal models [3,4]. These studies point to the need for establishing and characterizing animal models of OMN.

The hypogonadic (hgn/hgn) rat is characterized by male sterility due to testicular dysplasia during embryonic and postnatal development [9] and by reduced female fertility caused by a reduced stock of oocytes in the hypoplastic ovary [10]. The locus responsible for male sterility in this model has been mapped to rat chromosome 10 [11]. In addition to altered fertility, the phenotype of this mutant strain includes bilateral hypoplastic kidney (HPK: hpk/hpk).

In a previous study, we found that the HPK contains a smaller number of nephrons, resulting from reduced nephrogenesis during the period of prenatal and early postnatal renal development [12]. The plasma concentrations of urea nitrogen (UN) and creatinine (Cr) were elevated and the degree of renal histological damage progressed with advancing age in these rats. Renal anaemia, hyperparathyroidism and fibrous osteodystrophy appeared with advanced age [13]. These results suggest that the HPK is a useful model for studying the progression of renal damage resulting from a congenital reduction of nephrons. In contrast to other murine genetic models wherein the kidneys contain more than half the number of nephrons that exist in normal kidneys, HPK rats have less than one-quarter the number of nephrons [12], which is nearly equivalent to that reported in human OMN [2–4].

In this study, we compared water intake, urine volume, Cr and UN clearance (Ccr and Cun), glomerular number (GN), glomerular projective area (GPA) and blood pressure between adult HPK rats and phenotypically normal littermates (+/hgn or ++/++). Urinalysis for proteinuria and histological examination were also performed.

**Subjects and methods**

**Animals**

The hypogonadic (HGN) rat inbred strain was isolated from the sixth filial generation of a polygenic hydronephrotic rat strain derived from the original stock of the Wistar-Inamichi rat closed colony. Since the potential occurrence of hydronephrosis would have an influence on renal development and function, we established another hypogonadic (HGNII) rat strain that was derived directly from the original closed colony by experimental inbreeding. The HGNII strain has been maintained by inbreeding between carriers for 17 generations. Mating experiments for complementation tests revealed that the mutated gene responsible for hypogonadism in the HGNII strain is identical to that in the HGN strain. The affected rats of the HGNII strain show the same phenotype as that of the HGN strain with regard to hypogonadism and HPK, although the incidence of hydronephrosis in the HGNII strain is <0.2%. In this study, we used male rats derived from the HGNII strain. Adult HPK males were identified externally by palpation of the gonads for the detection of hypogonadism [9,12,13]. All rats were fed a certified commercial diet (CE-2; CLEA, Japan) and kept in a clean conventional animal room under controlled light conditions (14 h light, 10 h dark) [13]. Experimental procedures and care of animals were in accordance with the guidelines of the Animal Care and Use Committee of Nippon Veterinary and Animal Science University.

**Determination of Cr and UN clearance**

In order to assess Ccr and Cun, five HPK rats and five phenotypically normal littermates (+/hgn or ++/++) at 70 days of age were housed individually in plastic metabolic cages (TP-85M; Toyoriko, Tokyo). After they had been given 5 days to adapt to the cage, urine samples were collected in ice-cooled glass flasks every 8 h for 24 h and stored at 4°C. Urine samples from each rat were combined and measured. After centrifugation, aliquots of the supernatant were frozen at −20°C. Water intake was also measured. After collection of each urine sample, blood samples were collected from the jugular vein with a heparinized plastic syringe under overdose ether anaesthesia. Plasma samples were obtained and stored at −20°C. The plasma and urine Cr and UN concentrations were measured using previously reported methods [12,13].

**Determination of glomerular number**

In order to estimate the average value of single nephron Ccr, GN was determined in each rat that had Ccr measurement. Glomeruli were counted by HCl-maceration methods, as described previously [12]. The GN for individual rats was expressed as the total GN from both kidneys.

**Measurement of glomerular size**

In each experiment where we counted glomeruli in macerated renal samples, more than five photographs (including 8–22 glomeruli) were taken randomly under a light microscope at ×50 magnification (Nikon FX-35A; Nikon, Japan). The pictures were converted into digital data using a GT-5000ART scanner (Epson, Tokyo, Japan). The projective areas of all glomeruli appearing in the picture were measured using NIH Image (National Institute of Health, Bethesda, MD, USA). Both GN and glomerular size from each rat were expressed as the average of data from both kidneys. To display the variety of individual glomerular sizes in normal and HPK kidneys, all raw values from the measurements of GPA were plotted on a scattergraph (a total of 130 glomeruli).

**Measurement of blood pressure**

Tail-cuff blood pressures of eight normal and six HPK males at 70 days of age were measured using a computerized automated system (Softron, Tokyo, Japan) [14], according to manufacturer’s instructions. Rats were restrained in a holder maintained at 37°C and measurements were repeated for each rat three times per day during 5–10 consecutive days until the rats had adapted to the procedure.
Histological examination
Renal histology was examined at 35 and 70 days of age. Three HPK and three normal rats were sacrificed by ether overdose on these days. Their kidneys were removed, fixed in 4% neutral formalin, dehydrated in a graded alcohol series, embedded in paraffin and then sectioned at 3 μm thicknesses. The sections were stained with periodic acid and methenamine silver (PAM) [13]. They were then examined under a light microscope (BX50; Olympus, Tokyo) and images were obtained by a digital camera system (Pixcera Co., Osaka, Japan) attached to the microscope [9].

Electrophoresis of urinary protein
Frozen urine samples from 70-day-old rats were thawed, diluted and urinary protein concentration was measured by the BCA protein assay system (Pierce Biotech. Inc., Rockford, IL, USA). The diluted samples were added to an equal volume of 2× Tris–sodium dodecyl sulphate (SDS) sample buffer (Owl Scientific Inc., Woburn, MA, USA) and boiled for 3 min. Aliquots with 7 μg protein were loaded onto a 12.5% SDS–PAGE gel (mini gel: 10 × 10 cm). After electrophoresis, the gel was stained with 0.25% Coomassie Brilliant Blue solution. Gel images were obtained by a gel imaging system (Printgraph Atto Co., Tokyo, Japan) [9].

Urine albumin concentration
Urine samples were collected into test tubes by carefully pushing the abdomen of five HPK and eight normal males at 3, 7, 12, 21, 28 and 35 days of age and the samples were stored at −40°C. The concentration of urinary albumin was determined using an enzyme-linked immunosorbent assay system (Nephrat Exocell Inc., Philadelphia, PA, USA).

Statistical analysis
Differences between normal and HPK rats were tested using unpaired Student’s t-tests. Values are presented as means ± SEM.

Results
In the present study, we initially evaluated various renal function parameters involved in adult HPK in rats (Table 1). We found that body weight of HPK rats was significantly lower than in normal rats and that the relative kidney weight was apparently smaller in HPK rats compared with normal rats. HPK rats showed polyuria and polydipsia and their urinary volume was significantly larger compared with normal animals. Plasma UN levels were significantly higher in HPK rats than in normal rats. Plasma Cr was also high in HPK rats, although the difference was not statistically significant. Consistent with these findings, Ccr was lower in HPK rats than in normals. Cun was also significantly lower in HPK than in normal rats. Glomerular number, size and clearance are shown in Table 2. The kidneys from HPK rats had only 20% of the nephrons found in kidneys from normal rats. Thus, individual nephrons in HPK were estimated to be about three times heavier than nephrons in normal kidney. When Cun and Ccr were normalized to GN, HPK rats had levels of Cun and Ccr per single nephron that were about two and four times greater than in normal animals, respectively.

To evaluate the degree of glomerular hypertrophy in HPK rats, we measured the size of individual glomeruli during the determination of GN in macerated renal samples. GPA was significantly larger in HPK than in kidneys of normal rats. Total GPA of glomeruli (obtained by multiplying individual GPA by GN) was apparently smaller in HPK than in normal kidneys (Table 2). During the measurement of glomerular size, we found that HPK contained not only hypertrophied glomeruli, but also glomeruli of normal size (Figure 1A). The scattergram of raw values from individual GPAs indicated that HPK had a heterogeneous population of glomerular sizes (Figure 1B). Histological examination revealed that HPK had dilated tubules and hypertrophied glomeruli in the cortex, but that inflammation in the interstitium was not prominent (Figures 2A and 2B). The size and

### Table 1. Comparison of renal function between normal and HPK rats at 70 days of age

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal (n=5)</th>
<th>HPK (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Weights</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight (g)</td>
<td>309.2±24.4</td>
<td>214.7±6.6</td>
</tr>
<tr>
<td>Kidney weight (KW) (mg)*</td>
<td>2118.9±148.0</td>
<td>1271.8±57.7</td>
</tr>
<tr>
<td>Relative kidney weight (KW/BW)</td>
<td>0.87±0.10</td>
<td>5.92±0.19</td>
</tr>
<tr>
<td><strong>Water and food intake and urinary volume</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Water intake (ml/day)</td>
<td>34.3±4.5</td>
<td>44.1±8.8</td>
</tr>
<tr>
<td>Urinary volume (ml/day)</td>
<td>12.6±1.2</td>
<td>26.1±5.4</td>
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<td><strong>Clinical data related to renal function</strong></td>
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<td></td>
</tr>
<tr>
<td>Plasma UN level (mg/dl)</td>
<td>15.2±1.0</td>
<td>27.2±3.4</td>
</tr>
<tr>
<td>Plasma Cr level (mg/dl)</td>
<td>0.68±0.04</td>
<td>0.78±0.08</td>
</tr>
<tr>
<td>Ccr (ml/min)</td>
<td>1.19±0.07</td>
<td>0.83±0.16</td>
</tr>
<tr>
<td>Cun (ml/min)</td>
<td>1.45±0.15</td>
<td>0.60±0.08</td>
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Values are mean±SEM. BW: body weight, KW: kidney weight.
*Data shown are total values in the kidneys of both sides.
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### Table 2. Glomerular number, size, and clearance of normal and HPK rats at 70 days of age

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Normal (n=5)</th>
<th>HPK (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glomerular number (GN)*</td>
<td>44248±2225</td>
<td>7952±1143</td>
</tr>
<tr>
<td>Nephron weight (μg)*</td>
<td>48.7±5.1</td>
<td>175.4±30.7</td>
</tr>
<tr>
<td>Ccr/GN (μl/min)</td>
<td>0.027±0.002</td>
<td>0.106±0.020</td>
</tr>
<tr>
<td>Cun/GN (μl/min)</td>
<td>0.033±0.004</td>
<td>0.080±0.012</td>
</tr>
<tr>
<td>Glomerular projective area (μl²)</td>
<td>9614.3±843.9</td>
<td>19187.2±787.4</td>
</tr>
<tr>
<td>Total projective area (mm²)*</td>
<td>418.6±25.3</td>
<td>151.8±17.6</td>
</tr>
</tbody>
</table>

Values are mean±SEM. *Data shown are total values in the kidneys of both sides.
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### Notes

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histology of most glomeruli of surface nephrons appeared to be normal in HPK (Figures 2C and 2D). Most glomeruli in the inner cortex of the HPK appeared to be extremely hypertrophied and showed marked accumulation of mesangial matrix (Figures 2E and 2F). Furthermore, in the inner cortex of HPK, we found not only hypertrophied nephrons but also other slight pathological changes, such as dilation of collecting ducts and focal cellular infiltration in the interstitium (Figure 2F). In the medulla, HPK had hypertrophied and dilated tubules (Figures 2G and 2H).

Since total excretive functions of kidneys with reduced numbers of nephrons can be maintained by elevations in blood pressure that increase glomerular filtration rate (GFR) [4,8], we measured blood pressure using the tail-cuff method. However, there was no significant difference in blood pressure between normal and HPK rats (Table 3).

Urinary samples from adult HPK rats at 70 days of age showed proteinuria. Total protein excretion (mg/24 h) was higher in HPK rats (148.7 ± 36.0; n = 3) than in normal rats (71.6 ± 27.9; n = 3). In HPK, considerable leakage of albumin was found in the urine (Figure 3). Western blot analysis was also performed to confirm the presence of albumin (data not shown). Several protein bands with molecular weights >97.4 kDa were thought to be fragments of immunoglobulin G [15]. Since we could not obtain accurate or adequate urine volumes from the infant rats, we measured only urinary albumin concentration. Although albumin leaked from immature glomeruli at an early developmental stage in normal rats, albumin concentrations were significantly higher in HPK rats at 7, 21, 28 and 35 days of age (Figure 4). Since a remarkable leakage of albumin was present in the urine at 35 days of age, we examined renal histology at this age and found that
Discussion

This report demonstrated that kidneys of HPK rats contain an extremely reduced number of nephrons with extremely enlarged glomeruli and that HPK rats have levels of polydipsia, polyuria and proteinuria, a tendency for reduced GFR, growth impairment and both glomeruli and tubules were hypertrophied in HPK (Figure 5).
normal blood pressure that are similar to those reported in human OMN [2,3]. We previously reported that, in spite of severe reductions in nephron mass, HPK rats are viable but that they do progress to renal failure with age, which secondarily induces renal anaemia, hyperparathyroidism and osteodystrophy [13]. These secondary renal manifestations also have been reported in end-stage human OMN [2]. In this regard, HPK rats appear to be a more suitable model than other previously reported models that have mild forms of congenitally reduced nephron number [4,7,8], that have ≥50% of the nephrons that are present in normal animals and that do not progress to end-stage renal failure. Perinatal bcl-2-deficient mice have been shown to exhibit renal hypoplasia with extremely hypertrophied nephrons [16]. However, postnatal pathology in these mice includes alterations caused by polycystic kidney disease [1] and their phenotypes are more severe, with half of them dying by the sixth week of age.

In previous reports, we found that the HPK phenotype includes body growth impairment in both sexes, male sterility caused by testicular dysplasia [9] and early reproductive senescence in females caused by congenital ovarian hypoplasia [10]. Recent studies have suggested a relationship between birth weight and renal size (GN). These factors are thought to be related to the occurrence of cardiovascular diseases [3,4]. It has been reported that patients suffering from OMN experience not only small kidney size but also growth retardation [2–4]. At present, the causes of growth

![Fig. 3. Representative photograph showing SDS–PAGE of urinary samples from rats at 70 days of age. Diluted urine containing 7 μg protein was applied to each lane. The presence of albumin was confirmed by immunoblotting analysis. Note the considerable amount of albumin leakage from HPK. Mr, molecular-mass standards; each protein band from top to bottom corresponds to 97.4, 66.3, 42.4, 30, 20.1 and 14.4 kDa, respectively.](image)

![Fig. 4. Postnatal changes in urinary albumin leakage of normal and HPK rats. The values are means±SEM (vertical bars). *P<0.05.](image)

![Fig. 5. Histological photographs showing renal cortex of normal (A) and HPK (B) rats at 35 days of age (magnification: ×300). The juxtamedullary glomeruli were hypertrophied in HPK compared with those in normal kidneys. The diameters of tubular sections appeared to be larger in HPK. A slight accumulation of mesangial matrix was also observed in glomerulus of the HPK. Hypertrophied tubules were observed. PAM staining.](image)
Impairment in HPK rats and in human OMN are unclear. In some patients with Kallmann’s syndrome, hypogonadotrophic hypogonadism has been reported to be associated with growth retardation and congenital renal hypoplasia [17]. However, the hypogonadism in HPK is hypergonadotrophic hypogonadism. In contrast, Kleinfelter’s syndrome, which causes hypergonadotrophic hypogonadism in humans, is usually not associated with growth retardation and/or renal hypoplasia. Therefore, it is unlikely that growth retardation and/or renal hypoplasia are caused by hypogonadism in HPK. Although no reproductive defects have been reported in most cases of OMN in humans, the development of the gonads and kidneys are closely related by means of the mesonephros and some of the genes critical for normal development are common in the gonads and kidneys [1]. A reduced number of nephrons and defective growth of seminiferous tubules have been observed in neonatal hypogonadic rats [9,12]. In preliminary experiments, we found that hypoplasia of both organs and impairment of body growth were already visible at embryonic day 16.5 (data not shown). We have recently localized the responsible gene for hypogonadism to an 840 kb region on the physical map of rat chromosome 10 [18]. In the linkage analysis, we found that the affected (hypogonadic) backcross progeny showed renal hypoplasia and growth retardation under an altered genetic background [11,18]. These results indicate that the main responsible gene for HPK and growth impairment is identical to that which causes hypogonadism and that the gene is probably located in the same region of chromosome 10. At present, neither the loci responsible for reproductive disorders nor for renal failure have been mapped on the homologous regions of mouse chromosome 11 and human chromosome 17. Thus, a determination of the gene responsible for HPK and the hypogonadic phenotype would provide new insight to our understanding of the genetic aetiology of renal and gonad hypoplasia.

The elevated plasma UN and reduced Ccr and Cun levels indicated that HPK rats had a total reduction in total GFR. However, the average values of single nephron Ccr and Cun increased by about two and four times normal levels, respectively. Therefore, it is clear that individual nephrons have glomerular hypertrophy in HPK. Polyuria and polydipsia appeared in adult HPK rats. These symptoms have been described in newborn OMN [2]. In OMN, a reduced number of nephrons and defective growth of seminiferous tubules have been observed in neonatal hypogonadic rats [9,12]. In preliminary experiments, we found that hypoplasia of both organs and impairment of body growth were already visible at embryonic day 16.5 (data not shown). We have recently localized the responsible gene for hypogonadism to an 840 kb region on the physical map of rat chromosome 10 [18]. In the linkage analysis, we found that the affected (hypogonadic) backcross progeny showed renal hypoplasia and growth retardation under an altered genetic background [11,18]. These results indicate that the main responsible gene for HPK and growth impairment is identical to that which causes hypogonadism and that the gene is probably located in the same region of chromosome 10. At present, neither the loci responsible for reproductive disorders nor for renal failure have been mapped on the homologous regions of mouse chromosome 11 and human chromosome 17. Thus, a determination of the gene responsible for HPK and the hypogonadic phenotype would provide new insight to our understanding of the genetic aetiology of renal and gonad hypoplasia.

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Developmental generation age has been reported to be older in deep nephrons forming arcades than in surface (end-terminal) nephrons [1]. If the reduction in branching morphogenesis had occurred at an early stage of renal development, older generations of nephrons, which have entered into the maturation stage of glomerulogenesis, may be exposed to functional overload at the later stages of renal development. This may be the case since older nephrons function and produce urine during the period when the nephrogenesis of new generations of nephrons continues. This situation may change glomerular haemodynamics to induce alterations in gene expression during the process of glomerular maturation, resulting in the appearance of unusually enlarged glomeruli in older nephrons [20]. Such a process may protect later generations of nephrons from being exposed to altered haemodynamics (e.g. glomerular hypertension) during glomerulogenesis. In previous experiments, we found hypertrophy in older generations of glomeruli during postnatal nephrogenesis [12]. By contrast, the early cessation of late nephrogenesis during renal hypoplasia results in a thin cortex layer that may give rise to different phenotypes with regard to glomerular hypertrophy and hypertension.

The present report is the first demonstration of a correlation between glomerular hypertrophy and hyperfiltration in the HPK rat model of human OMN, indicating that the HPK rat may be a useful model for studying the pathophysiology of OMN as well as glomerular hyperfiltration and hypertension induced by a severe congenital reduction of nephrons. In future studies, we will focus on the molecular basis of the pathogenesis of renal hypoplasia and will analyse alterations of gene expression induced by the congenital reduction of nephron number in the HPK. In addition, HPK rats seem to have a strong potential as a tool for understanding the pathophysiology of chronic renal failure and for the development of drugs to prevent the progression of renal failure.

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References


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