Pathophysiology and Postnatal Pathogenesis of Hypoplastic Kidney (*hpk/hpk*) in the Male Hypogonadic Mutant Rat (*hgn/hgn*)

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(Received 6 February 1995/Accepted 27 June 1995)

ABSTRACT. The male hypogonadic rat (*hgn/hgn*) is accompanied with bilateral hypoplastic kidney (HPK; *hpk/hpk*) [34]. In this study, we examined the kidney weight (KW), glomerular number (GN), renal pathohistology at adult (80 days of age), and pathogenesis during the early postnatal stage in the *hpk/hpk*, *+hpk*, and *+/+* rat. The GN of adult *hpk/hpk* was significantly less than that of the *+hpk* and *+/+*. Histologically, there were the decreased number of nephrons and the associated secondary changes in the *hpk/hpk* kidney. The plasma concentrations of urea nitrogen and creatinine were significantly higher in the *hpk/hpk* than in the *+hpk* and *+/+*. During early postnatal stage, the KW of the *hpk/hpk* was significantly smaller than those of the *+hpk* and *+/+*, and the GN was fewer in order of the *hpk/hpk*, *+hpk* and *+/+*, showing the significant differences between given genotypes. The layer of nephrogenic nephron beneath the renal capsula of the neonatal kidney appeared to be thinner in the *hpk/hpk* than in the normal (*+hpk* and *+/+*). In the *hpk/hpk* kidney on 3 days of age, the layer of the nephrogenic nephron was absent in some portions beneath the renal capsula. In the *hpk/hpk* kidney on 7 days of age, further, the layer of immature type of nephron was still observed under the capsula. These studies suggest that the hypoplastic kidney, which may result from reduced nephrogenesis, could not compensate the renal weight, GN and renal function during the postnatal nephrogenic stage.—**KEY WORDS:** hypogonadism, kidney, mutant, rat, renal hypoplasia.

J. Vet. Med. Sci. 57(5): 891–897, 1995

The male hypogonadic (*hgn/hgn*) mutant rat, found at our department in 1984, has been maintained by sister-brother mating of the carriers. It has been characterized by genetic mode of transmission as an autosomal recessive, normal karyotype (40 + XY), testicular abnormal morphology, and low testosterone and high gonadotropin levels in the serum [16, 33]. Recently, it has been revealed that the male hypogonadism is constantly accompanied with the bilateral hypoplastic kidney (HPK; *hpk/hpk*), and that the *hgn/hgn* females identified by the presence of HPK have a reduced fertility [30, 34]. These studies suggested that the gene *hgn* and *hpk* would be identical or reside in the close vicinity in a chromosome, and revealed that the bilateral HPK in the *hgn/hgn* is a new hereditary disease of rat with a single autosomal recessive trait.

Renal hypoplasia has been reported in various animals including humans [3, 18, 39], but the early pathogenesis of the renal hypoplasia has not been described. In order to study an early stage of the pathogenesis of the renal hypoplasia, animal models, either inherited or experimentally induced, would be needed. The newly found HPK rat may be a unique tool for studying both the development of renal hypoplasia and pathophysiological state in such conditions. In this study, in adult *hpk/hpk* and normal rats the number of glomeruli (GN), urea nitrogen (UN) and creatinine levels in the plasma were measured and kidneys of these rats were histopathologically examined. In addition, the postnatal renal changes were observed in the *hpk/hpk*, *+hpk* and *+/+* rats on days 0 to 18 of age.

MATERIALS AND METHODS

Animals: Male rats from three genotype groups (*+/+*, *+hpk*

and *hpk/hpk*) in the 17th generation of the male hypogonadic rat (HGN) line were used in this study [33]. The *hpk/hpk* males were identified by the presence of HPK and hypogonadism [34]. The *+hpk* were the phenotypically normal animals obtained by the mating between the *+hpk* males and *hpk/hpk* females [30, 34]. Since the *+/+* animals can not be phenotypically distinguished from the *+hpk* rats, adult *+/+* rats were defined as animals that had produced more than 11 normal pups without any affected when mated with the *+hpk*. The immature assumptive *+/+* rats were obtained from the mating between assumptive *+/+* males and females. The rats were bred and fed under the same condition as described in previous reports [16, 32, 33].

Number of glomeruli (GN): Three animals in each genotype group were sacrificed on days 3, 7, 12, 18 and 80 after birth and used for counting GN according to the method described by Josephson [19]. Briefly, 1 ml of indian ink per 200 g of body weight was injected from the jugular vein exposed under light ether anesthesia. The rat was sacrificed by decapitation immediately after the skin color became dark, and bilateral kidneys were removed. After renal decapsulation, the kidneys were weighed at the nearest 0.1 mg and cut into a few slices. The slices from each kidney were then digested in 4 volume of 8 M HCl against kidney weight at room temperature under gentle agitation until the visible pieces of renal tissue were lost. The digestion was stopped by addition of appropriate volume of physiological saline into the glomerular suspension. The suspension volume was finally measured up to defined value according to the original size of the kidney. Fifty μ l of the suspension was placed carefully on a slide glass to be spread to an appropriate area. The glomeruli containing the particles of indian ink in the whole area were counted under

a light microscope. Only the mature glomeruli supplied by blood vessels were counted at early postnatal stages (3 and 7 days of age) when the immature glomeruli at various stages of development existed in the kidney. The GN of the individual rat was expressed as the average of the GN of 2 kidneys on both sides.

Histological examination of kidney: Another 3 animals in each genotype group were sacrificed by over dose ether on days 0, 3, 7, 12 and 80 after birth. The removed kidneys were fixed in 4% neutral formalin, dehydrated with graded alcohol, embedded in paraffin, and sectioned at 3 μ m. The sections were stained with periodic acid Schiff (PAS) reaction and hematoxylin, and examined under a light microscope.

Measurement of UN and creatinine levels: Four adult male animals from each genotype group were used. Blood samples were collected from the jugular vein with a plastic syringe moisturized with a small amount of heparin. Plasma samples were obtained by centrifugation and stored at -40°C until the measurement. Plasma UN and creatinine levels were measured using Fearon reaction (UreaN-Test, Wako) [9] and Jaffe reaction (creatinine-Test, Wako) [4], respectively.

Statistical analysis: Student's *t*-test was used for the statistical analysis of the data, being significant at $p < 0.05$.

RESULTS

Kidney weight (KW) and GN at adult (80 days old): KW and GN of the *hpk/hpk* were significantly smaller than those of the *+hpk* and *+/+*, respectively. GN/KW of the *hpk/hpk* was significantly less than that of the *+hpk* and *+/+* (Table 1). There was no significant difference in any parameter between the *+hpk* and *+/+*.

Histology of the adult kidney: Figure 1 shows the renal histology of the *+hpk* and *hpk/hpk* at adult (80 days old). In the *+hpk*, the three layers of renal cortex, outer- and inner- medulla could be easily distinguished each other and many glomeruli uniform in shape were scattered in the cortex at a constant density (Fig. 1A). In the *hpk/hpk* kidney, however, the layer structures could not be distinguished one another. Furthermore, the glomeruli of *hpk/hpk* kidney were obviously small in population and some hypertrophied glomeruli and tubules were observed (Fig. 1B). In comparison with *+hpk* kidney (Fig. 1C), glomeruli of *hpk/hpk* are varied in size and shape. Dilatation of Bowman's capsular lumen, increase in areas of

glomerular capillaries, thickening of Bowman's pericapsular wall, and glomerular sclerosis were observed in the *hpk/hpk* kidney. In addition, dilatation of tubular lumens was more remarkable in the distal portion of nephron, containing occasionally degenerated or desquamated renal epithelia. The lumens with hyalin casts were sometimes seen and inflammatory cells infiltrated into some portions of the interstitial tissue (Fig. 1D). No noticeable changes could be found between the *+hpk* and *+/+*.

Plasma UN and creatinine levels at adult (80 days old): The UN levels were the highest in the *hpk/hpk* then followed by the *+hpk* and *+/+*, and the values in each group differed significantly from each other. The creatinine levels were significantly higher in the *hpk/hpk* than in the *+/+* (Table 2).

Changes in KW and GN during early postnatal development: To demonstrate that a decrease in GN observed in adult *hpk/hpk* would not result from the loss of nephrons after completion of postnatal renal development but from nephronic hypoplasia, the postnatal changes of KW and GN were examined. The changes of KW and GN on 3 to 18 days are shown in Figs. 2 and 3, respectively. The KW of the *hpk/hpk* was significantly smaller than that of the *+hpk* and *+/+* in all days of age examined. The KW of the *+hpk* was significantly smaller than that of *+/+* on days 3 and 7. In any day of age examined, the *+/+* had the largest GN, followed by the *+hpk* and *hpk/hpk*, with significant differences in all possible combinations.

Histological examination of early postnatal kidney: To obtain the morphological evidences supporting significantly lower GN in the *hpk/hpk* kidney during early postnatal period, renal changes were histologically examined. At birth, there was the layer of nephrogenic nephrons beneath the capsula in the *+/+*, *+hpk* and *hpk/hpk*, although the layer of the *hpk/hpk* appeared to be thinner than that of the *+/+* and *+hpk*. Therefore, the nephrogenic nephron of the *hpk/hpk* appeared to be smaller in population than that of the *+/+* and *+hpk*. More mature nephrons were observed under the nephrogenic layer in the kidney of all groups, but these nephrons appeared to be smaller in population in *hpk/hpk* than in *+/+* and *+hpk* (Fig. 4A, B, C). On 3 days of age, a number of nephrogenic nephrons including renal vesicle and S-shaped body delineated the outermost area beneath the capsule in the *+/+* and *+hpk*. In the *hpk/hpk* kidney, however, the nephrogenic nephrons were absent

Table 1. Kidney weight (KW) and glomerular number (GN) of *+/+*, *+hpk* and *hpk/hpk* at adult (80 days old)

Genotype	KW (mg)	GN	GN/KW
<i>+/+</i>	1108.2 $\pm$ 170.6	27764 $\pm$ 2407	23.0 $\pm$ 6.2
<i>+hpk</i>	1085.0 $\pm$ 96.6	20252 $\pm$ 2797	18.6 $\pm$ 1.2
<i>hpk/hpk</i>	826.6 $\pm$ 86.3 ^{a)}	6270 $\pm$ 1077 ^{a)}	10.2 $\pm$ 2.6 ^{a)}

Each value represents mean $\pm$ S.D.

a) Significantly different from *+/+* and *+hpk* at $p < 0.05$.

Table 2. Urea-nitrogen (UN) and creatinine levels in plasma of *+/+*, *+hpk* and *hpk/hpk* at adult (80 days old)

Genotype	UN (mg/dl)	Creatinine (mg/dl)
<i>+/+</i>	19.0 $\pm$ 1.8	0.64 $\pm$ 0.27
<i>+hpk</i>	27.8 $\pm$ 5.5 ^{a)}	0.73 $\pm$ 0.55
<i>hpk/hpk</i>	56.4 $\pm$ 9.4 ^{b)}	1.04 $\pm$ 0.16 ^{a)}

Each value represents mean $\pm$ S.D.

a) Significantly different from *+/+* at $p < 0.05$.

b) Significantly different from *+/+* and *+hpk* at $p < 0.05$.

Fig. 1. Histology of adult *+/hp*k (A, C) and *hpk/hpk* (B, D) kidney. (A, B: $\times 33$, C, D: $\times 81$) A: Renal cortex and medulla can be easily distinguished each other. B: It is difficult to recognize the boundary between the cortex and medulla. A smaller number of glomeruli are present. C: Higher magnification of A. D: Higher magnification of B. Glomeruli are varied in size and shape. Various types of pathological alterations are observed.

Fig. 2. Postnatal changes of the average weight of the bilateral kidney in *hpk/hpk*, *+/hp*k and *+/+*. a: significantly different from *+/+* at $p < 0.05$. b: significantly different from *+/hp*k at $p < 0.05$.

Fig. 3. Postnatal changes of glomerular number in *hpk/hpk*, *+/hp*k and *+/+*. The counting method is described in "Text". a: significantly different from *+/+* at $p < 0.05$. b: significantly different from *+/hp*k at $p < 0.05$.

Fig. 4. Histology of sub-renal capsular area at 0 (A, B, C) and 3 (D, E, F) days of age (A, D: +/+, B, E: +/-hpk, C, F: hpk/hpk, $\times 81$). At birth, the nephrogenic layer appears to be thinner in the hpk/hpk kidney (C) than in the +/+ (A) and +/-hpk (B). In the hpk/hpk kidney on 3 days of age (F), the nephrogenic nephrons are absent in most of the portions beneath the renal capsula and undifferentiated mesenchymal cells (arrowheads) exist beneath the capsula and directly attach to the renal tubules. In addition, some of the proximal, distal and collecting tubules are dilated extremely in the hpk/hpk kidney (arrow). d: differentiating glomerulus, r: renal capsula, i: interstitial tissue.

beneath the capsule and undifferentiated mesenchymal cells existed between the capsule and adjoining tubules. Dilated renal tubules were sporadically observed in the hpk/hpk kidney (Fig. 4D, E, F). On day 7, in the normal kidney (+/+), superficial glomeruli have almost completed the differentiation into mature type, while in the hpk/hpk a number of glomeruli appeared at less differentiated stages in the superficial area (Fig. 5A, B, C). These immature glomeruli of the hpk/hpk developed into mature type by day 12. The luminal dilatation in the hpk/hpk kidney was also remarkable on days 7 and 12. On day 12, the glomeruli in the hpk/hpk were much more hypertrophic as compared with those of the +/+ and +/-hpk (Fig. 5D, E, F). No morphological difference could be found between the +/+

and +/-hpk during this period.

DISCUSSION

The present study revealed that the postnatal KW and GN were significantly smaller in the hpk/hpk than in the normal, and that the renal excretive function was depressed in the adult hpk/hpk. In addition, the pathohistological features seen in the HPK resembled those of renal hypoplasia reported previously [3, 18, 39]. Glomerular sclerosis, inflammatory lesions and dilated tubular lumens with occasional hyaline casts observed in adult hpk/hpk kidney were considered to develop secondarily, as reported in the human and canine renal hypoplasia [3, 17, 21, 39].

Fig. 5. Histology of sub-renal capsular area on 7 (A, B, C) and 12 (D, E, F) days of age. (A, D: +/+, B, E: +/hpk, C, F: hpk/hpk, $\times 81$). In the hpk/hpk on 7 days of age (C), immature type of glomerulus at early stage of nephrogenesis is still observed beneath the capsula. Luminal dilatation of nephron and collecting tubules are remarkable in the hpk/hpk kidney. On 12 days of age, these immature glomeruli of the hpk/hpk (F) develop into the mature type as seen in the +/+ (D) and +/hpk (E). Individual nephron in the hpk/hpk is markedly hypertrophic. d: differentiating glomerulus, r: renal capsula, i: interstitial tissue.

However, the evidence that some of the nephron showed a dilatation of the lumen as early as 3 days of age suggests that the abnormalities in the HPK might also include anomalies of the renal dysplasia and polycystic kidney [3, 26, 39].

The inherited renal diseases, such as dysgenesis of one kidney associated with the defects in ureter and gonad [14, 15], hydronephrosis developing with polygenic trait [31, 37] and polycystic kidney associated with defects in skeletal structure [27], have been reported in rats. None of these renal diseases resemble the abnormalities in the HPK examined in this study in that the HPK inherited with a single autosomal recessive trait, affected both kidneys, included reduced number of nephrons (glomeruli) without the defect of ureter, and did not include the macroscopic

renal cyst. The bilateral renal hypoplasia has been described in humans and Cocker Spaniel dogs [3, 18, 39]. The histology of oligomeganephronie, described as the congenital renal hypoplasia in humans, resembles that of HPK to the point that there includes the significantly decreased number of hypertrophic nephrons [11]. The genetic etiology of this human HPK remains undetermined [22, 38]. In humans, the familial small kidney inherited with autosomal recessive or dominant trait has also been categorized into a type of renal dysplasia [1, 8, 20]. The renal hypoplasia of Cocker Spaniel dogs has been reported as a genetic etiology. The histological changes of this defect are restricted only in the renal cortex, suggesting the cessation of nephrogenesis at early stage [17, 21, 28].

The GN of the hpk/hpk averaged about one-third of the

+/hpk or one-fourth of the *+/+*. This suggests that the gene *hpk* might determine the GN. However, the other genetic factor(s) affecting the GN might exist in the HGN line, since the GN of the *+/+* was significantly less than that of rats in our closed colony ($36,017 \pm 2,969$, unpublished data). The KW of adult *hpk/hpk* averaged about a half of that of both *+/+* and *+/hpk*. Significantly decreased GN/KW of the *hpk/hpk* would indicate the increase in the weight of an individual nephron. In general, it has been known that the decrease of total number of functional nephron in the renal disease or partial excision of renal tissue might induce the compensatory hypertrophy in the remaining tissues (glomerular hypertrophy and tubular elongation) with frequent secondary changes, resulting in the final stage of renal failure [2, 10, 11, 17, 21, 23, 28, 29]. The similar conditions possibly resulting from the reduced nephrogenesis would exist in the present HPK and become more remarkable with an advancing age. In the *hpk/hpk*, the individual nephron was histologically hypertrophic on the 12 days of age and degenerative changes in the glomeruli and tubules existed in the adult kidney. Significantly higher plasma levels of UN and creatinine in the adult *hpk/hpk* suggest that the renal excretive function could not be compensated completely by the renal hypertrophy. However, these levels of UN and creatinine were considerably low in view of that the number of nephrons in the *hpk/hpk* was about only one-fourth of the *+/+*. Recently we have demonstrated that HPK progressed finally to chronic renal failure and induced secondarily renal anemia and hyperparathyroidism [36]. Therefore, this mutant would be an useful model for studying the pathophysiological mechanisms by which the renal hypoplasia destined to the renal failure.

It has been known that the renal cortex of normal rat during the early postnatal stage contains various types of nephrogenic nephrons, all of which differentiate into the functional nephrons with the mature type of glomeruli by 10 days of age [12, 24, 25]. The GN of *+/hpk* and *+/+* rat increased rapidly after birth and achieved to the level of adult kidney on 12 days of age. The GN of the *hpk/hpk* was significantly less than that of both *+/hpk* and *+/+*, and the GN of the *+/hpk* was significantly less than that of the *+/+* during the early postnatal stage (3–18 days after birth). In general, the expression of a recessive gene in the heterozygotes is blocked by the expression of the dominant allelic gene. There was no significant difference between *+/hpk* and *+/+* in the KW after 12 days of age.

The smaller number of glomeruli and the absence of the nephrogenic layer in the *hpk/hpk* kidney on 3 days of age might result from smaller population of the mature and nephrogenic nephrons at birth and absence of induction of nephrogenic nephrons (initiation of nephrogenesis) during the period from 0 to 3 days of age, respectively. However, the induction of nephrons in the *hpk/hpk* kidney was restarted between 3 and 7 days of age and newly induced nephrons developed into the mature type of nephron by 12 days. These situations may cause the gradual increase in GN per whole kidney of the *hpk/hpk* during the early

postnatal period. If the existence of the immature type of nephrons at later stage in the *hpk/hpk* kidney might not result from delayed and incomplete maturation of nephrons caused directly by the *hpk* gene, this could be explained by similar phenomena seen in the increase of GN in the animals that lost one kidney at early postnatal stage: this condition has been attributed to compensatory mechanisms [5, 6].

From morphological evidences, the etiology of renal hypoplasia has been attributed to (i) an insufficient amount of metanephric blastoma available for renal development, (ii) insufficient early duct branching, (iii) reduced induction of nephrons during the period of arcade and superficial nephron production (resulting in the thinner cortex), and (iv) a retardation in the postnatal tubule and glomerular enlargement [39]. No renal hypoplasia categorized into (i) and (ii) has been reported [39]. The etiology of the present HPK (*hpk/hpk*) might fall into the categories of (i) and/or (ii). To determine the exact etiology of the HPK, morphometrical analysis is now in progress.

The present study suggested that the *hpk* gene should be expressed in the kidney at perinatal period, which might determine the number of mature nephrons. The state of *hpk/hpk* shows not only renal hypoplasia but also hypogonadism (*hgn/hgn*) causing sterility in males and reduced fertility in females [16, 30, 33–35]. The developmental processes of the kidney and gonad are closely linked by means of mesonephrons, which has been reported to donate cells to the embryonic gonadal anlagen and to secrete substances controlling the onset of meiosis [7, 13, 39]. Relation between assumptive genes *hpk* (kidney) and *hgn* (gonad) should be investigated by further studies. The *hgn/hgn* (*hpk/hpk*) rat would become an interesting tool for studies on the developmental physiology of the urogenital organs and the pathogenesis of renal hypoplasia.

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