J. Physiol. (1973), **228**, *pp.* 193–202
With 3 *text-figures*
Printed in Great Britain

COMPENSATORY RENAL GROWTH AFTER UNILATERAL NEPHRECTOMY IN THE NEW-BORN RAT

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(*Received 21 July 1972*)

SUMMARY

1. The right kidney in a series of control rats aged between 5 days and 115 days was weighed. The kidney weight/body weight ratio was greater in young than in older rats, but decreased linearly with increasing age.

2. After unilateral nephrectomy of rats 5 days old, the remaining kidney underwent compensatory growth. The rate and extent of this growth were greater than in adult rats.

3. The concentrations of RNA and DNA in the renal cortex and medulla of rats 5 days old were higher than in adult animals. The concentrations of the two nucleic acids fell with age, and reached adult levels after approximately 6 weeks.

4. After unilateral nephrectomy of rats 5 days old, the concentrations of RNA and DNA in the medulla were not significantly different from those in control animals. In the cortex, however, there was a delayed increase in the RNA/DNA ratio, which reached a level some 12 % higher than that in control rats. This increase was smaller than that observed in unilaterally nephrectomized adult rats.

5. The cortical Q_{O_2} of the remaining kidney of unilaterally nephrectomized new-born rats was elevated by some 20 % within 1 day of unilateral nephrectomy. Cortical Q_{O_2}'s remained higher than those of control animals for 3–4 weeks.

6. Since after unilateral nephrectomy, the increase in renal mass in newborns was greater than that in adults, whereas the degree of cortical cellular hypertrophy (as estimated by the RNA/DNA ratio) was smaller than in adults, it is likely that in new-born animals a significant contribution to compensatory growth comes from cellular hyperplasia.

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INTRODUCTION

In most mammals unilateral nephrectomy results in compensatory growth of the remaining kidney. The investigations of Arataki (1926), Jackson & Shiels (1927), Moore (1929) and Oliver (1944–45), in both adult and new-born animals, established that compensatory renal growth was the results of an increase only in the size of nephrons, not in their number. This enlargement of nephrons is achieved by a combination of cellular hypertrophy and cellular hyperplasia (Rollason, 1949; Anderson, 1967). An estimate of the relative contributions of cellular hypertrophy and hyperplasia can be obtained by estimating changes in the contents of nucleic acids and other cellular components in the remaining kidney. Such studies have indicated that in adult animals the first response to unilateral nephrectomy is an increase in cell size (Halliburton & Thomson, 1965; Johnson & Vera Roman, 1966; Malt & Lemaitre, 1968), which is confined mainly to the cortex (Dicker & Shirley, 1971*b*).

Though it has been stated that compensatory renal hypertrophy is greater in young than in adult animals (MacKay, MacKay & Addis, 1932; Verzár & Hügin, 1957), some investigators have either found the opposite to be the case (Arataki, 1926) or have been unable to detect any difference between the responses in young and older animals (Braun-Menéndez, 1946).

The purpose of the present investigation was to determine the extent of the compensatory renal response in the neonate, and to find whether the nature of this response was similar to that of adult animals.

METHODS

Male white rats ranging in age from 5 to 115 days were used. All operations were performed on neonates 5-days old. With the animals under ether anaesthesia, a small lumbar incision was made, and the left kidney was removed. In sham operated animals, the left kidney was exposed and gently manipulated but left intact. After the operation animals were returned to their mothers.

Estimation of renal hypertrophy. Kidney weights were expressed as mg/100 g body weight.

Renal hypertrophy was estimated by comparing the weight of the right kidney with that of the right kidney from control and sham-operated animals of the same age and similar body weight.

Estimation of oxygen uptake. Rates of oxygen uptake (Q_{O_2}) were measured in slices from renal cortex and medulla, using a Warburg apparatus (Dicker & Shirley, 1971*a*). Values for Q_{O_2} were expressed as μl. hr^{-1}. mg^{-1} dry weight.

Estimation of RNA and DNA. RNA and DNA were estimated separately in the renal cortex and medulla. The methods followed those described by Dicker & Shirley (1971*b*). In neonates under 4 weeks of age the kidneys were too small for the cortex to be dissected easily from the medulla; outer kidney slices, cut with a razor, were used as cortex, and the remainder of the kidney, with its cortical edges removed, was used as medulla. In these animals, cortical or medullary fractions from several rats were pooled.

Water content. Slices of renal cortex and medulla were weighed, then dried at 104° C for 48 hr.

Diet. All animals older than 3 weeks were fed on a standard diet containing approximately 18 % casein and yielding about 300 cal/100 g. Until this age, the rats were suckled by their mothers.

RESULTS

The rate at which body weight increased in unilaterally nephrectomized and sham-operated new-born rats was similar to that of control animals; as for kidney weights there was no difference between those of sham and unoperated rats. The rate of growth of the right kidney of control animals was not linearly related to their age (Fig. 1*a*). When, however, the kidney weights, expressed as mg/100 g body wt. were related to age, there was a linear correlation up to the age of 120 days, with a regression coefficient = $-2{\cdot}73 \pm 0{\cdot}105$ (Fig. 1*b*). Kidney weights of unilaterally nephrectomized rats (mg/100 g body wt.) were compared with those of control rats of similar age. After unilateral nephrectomy there was a marked increase in the weight of the contralateral kidney, and from 9 days after the operation the magnitude of renal compensatory hypertrophy was greater than that observed in adults (Fig. 2). The water content of kidneys of unilaterally nephrectomized rats was similar to that of sham operated and control neonates: it decreased with age up to 3 weeks after the operation when it reached its adult level (Dicker & Shirley, 1972).

The concentrations of RNA and DNA in the renal cortex and medulla of control rats 5 days old were about twice as high as in adult rats. Their concentrations fell, however, to adult levels in 6–10 weeks in both regions of the kidney (Fig. 3*a*, *b*); in the cortex this was accompanied by an increase in the RNA/DNA ratio from 1·00 to 1·25, while in the medulla the RNA/DNA ratio fell from 1·00 to 0·90. The renal nucleic acid concentrations in sham-operated new-born rats were similar to those in control animals. After unilateral nephrectomy, RNA and DNA concentrations in the medulla of the remaining kidney did not differ significantly from those in sham-operated new-born rats. In the cortex, RNA values decreased slowly but became significantly lower than those in sham-operated animals only 65 days after the operation ($P < 0{\cdot}05$). In contrast, DNA concentrations decreased much more rapidly, being already 13 % below the level in sham-operated animals after 6 days. These changes in RNA and DNA in the cortex of the remaining kidney of unilaterally nephrectomized neonates resulted in a rise in the RNA/DNA ratio which after 6 days was some 12 % higher than that of sham-operated animals. This difference did not change significantly throughout the whole period of observation. The increase in the RNA/DNA ratio was much smaller than that found in adult animals (Dicker & Shirley, 1971*b*).

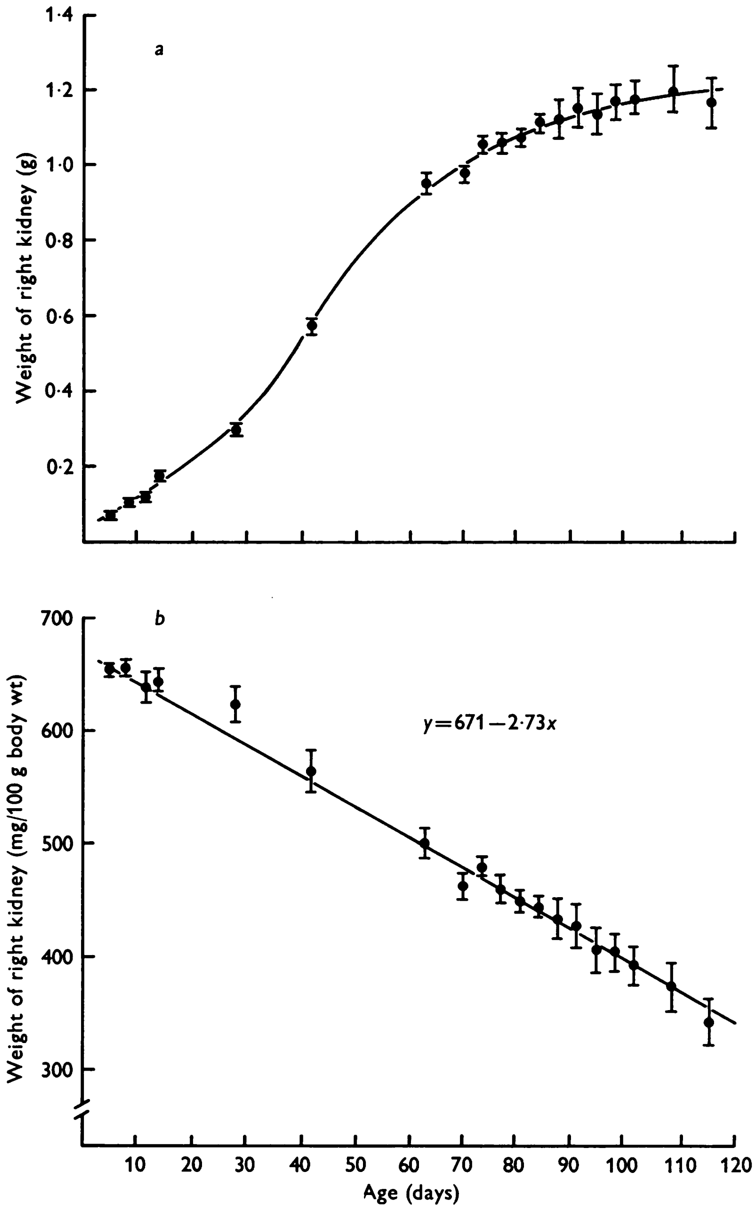

Fig. 1. Comparison of weight of right kidney with age in new-born and growing male rats. Upper graph (*a*): kidney weight (g) against age. Lower graph (*b*): kidney weight, expressed in mg/100 g body wt., against age. The regression line of kidney weight/100 g body wt. on age is shown. Each point and vertical line represents the mean ± S.E.

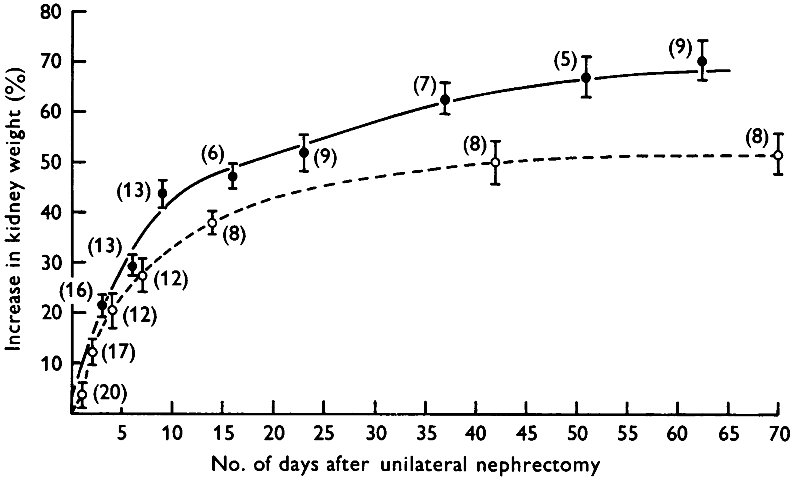

Fig. 2. The rate of compensatory renal growth following unilateral nephrectomy of 5-day-old and adult rats. Percentage change in the wet weight of the contralateral kidney: ●——● after unilateral nephrectomy of rats 5-days old; ○ - - - - - ○ after unilateral nephrectomy of adult rats. Abscissa: number of days after unilateral nephrectomy. Ordinate: percentage change in kidney wet weight (see text). Vertical lines represent the S.E.'s of the means. Figures in parentheses: number of animals.

TABLE 1. Rates of oxygen uptake (Q_{O_2}) by slices of renal cortex and medulla from unilaterally nephrectomized and sham-operated new-born rats

No. of days after operation	Q_{O_2} (µl./hr. mg dry tissue) Unilaterally nephrectomized rats		Sham-operated rats	
	Cortex	Medulla	Cortex	Medulla
0	10·16 ± 0·21 (17)	10·43 ± 0·31 (14)	10·16 ± 0·21 (17)	10·43 ± 0·31 (14)
1	12·62 ± 0·26 (6)	9·74 ± 0·38 (6)	10·72 ± 0·36 (6)	9·87 ± 0·39 (6)
3	13·12 ± 0·15 (6)	9·62 ± 0·38 (6)	11·26 ± 0·45 (6)	9·68 ± 0·58 (6)
6	13·63 ± 0·24 (6)	9·14 ± 0·37 (6)	11·59 ± 0·37 (6)	8·88 ± 0·44 (6)
9	13·51 ± 0·41 (9)	8·81 ± 0·48 (9)	11·76 ± 0·41 (9)	9·04 ± 0·36 (8)
16	13·64 ± 0·39 (9)	8·10 ± 0·34 (9)	11·97 ± 0·39 (9)	8·04 ± 0·45 (8)
23	13·32 ± 0·20 (9)	8·07 ± 0·36 (9)	12·92 ± 0·49 (9)	7·95 ± 0·32 (9)
37	13·03 ± 0·45 (5)	8·70 ± 0·52 (5)	12·75 ± 0·37 (6)	8·41 ± 0·51 (5)
65	13·09 ± 0·29 (6)	8·20 ± 0·36 (6)	13·42 ± 0·46 (6)	8·37 ± 0·37 (6)

Values are given as means ± S.E. Number of estimations in parentheses. All surgical operations were performed on animals 5 days old. Values for day 0 are those for unoperated rats 5 days old.

Values for Q_{O_2} in both the cortex and medulla of sham-operated animals were comparable with those found in unoperated controls: Q_{O_2} values in the cortex increased with age from $10{\cdot}16 \pm 0{\cdot}21$ (17) in 5-day-old rats to $13{\cdot}42 \pm 0{\cdot}46$ (6) μl. $hr^{-1}.mg^{-1}$ dry tissue 65 days later, while in the medulla Q_{O_2} values fell from $10{\cdot}43 \pm 0{\cdot}31$ (14) to $8{\cdot}37 \pm 0{\cdot}37$ (6) μl $hr^{-1}.mg^{-1}$ dry

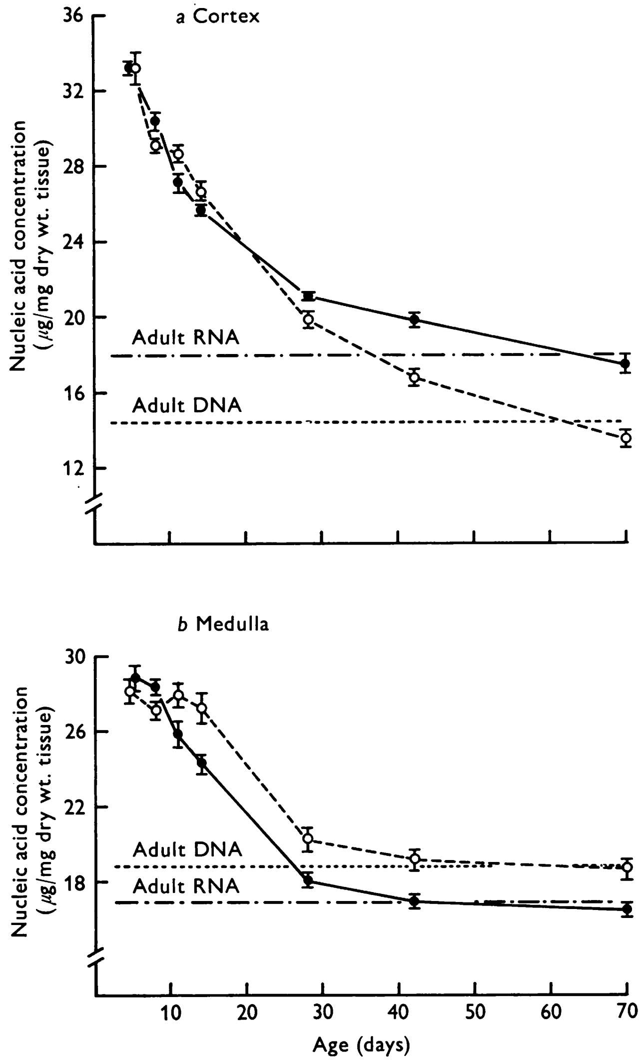

Fig. 3. RNA and DNA concentrations in renal cortex and medulla of control rats aged between 5 days and 10 weeks. RNA concentration: ●——●; DNA concentration: ○--- ○. Abscissae: age in days. Ordinates: nucleic acid concentration (μg/mg dry wt. of tissue). All points are means $\pm$ S.E. Number of estimations: 12 for 5-day old rats, 4 for the others.

tissue, in the same time. In contrast, in unilaterally nephrectomized rats, Q_{O_2} values in the cortex increased very quickly, and within 24 hours of the operation were about 20% above the levels found in sham-operated animals. This difference had disappeared in 5 weeks (Table 1). Q_{O_2} values in the medulla of unilaterally nephrectomized neonates were much the same as those in sham-operated animals (Table 1).

TABLE 2. Rates of oxygen uptake per cell (estimated as Q_{O_2}/DNA) in the renal cortex and medulla of unilaterally nephrectomized and sham-operated new-born rats

No. of days after operation	Q_{O_2}/DNA (µl./µg)			
	Unilaterally nephrectomized rats		Sham-operated rats	
	Cortex	Medulla	Cortex	Medulla
0	0·31	0·37	0·31	0·37
3	0·46	0·33	0·39	0·33
6	0·54	0·31	0·40	0·33
9	0·59	0·32	0·45	0·35
23	0·79	0·38	0·66	0·36
37	0·90	0·47	0·79	0·45
65	1·13	0·47	0·95	0·45

Values given were calculated from mean values of Q_{O_2} (Table 1) and of DNA concentration. Values at day 0 are those from unoperated 5-day-old rats.

Since, according to Vendrely (1955), in renal cells the DNA content per nucleus appears to be constant, the DNA content can be taken as a measure of cell number. It is therefore possible to calculate the average Q_{O_2} per cell in normal and renoprival kidneys. Table 2 shows the cellular Q_{O_2}'s of the renal cortex and medulla of unilaterally nephrectomized and sham-operated rats. It can be seen that after unilateral nephrectomy, whereas the oxygen uptake per cell in the medulla of the remaining kidney is at all times similar to that of the kidneys of sham-operated rats, in the cortex there is a marked increase in the amount of oxygen consumed per cell.

DISCUSSION

The results of the present investigation have shown that between the ages of 5 and 115 days there is in the rat a linear relationship between the kidney weight/body weight ratio and age. This confirms and extends the work of MacKay & MacKay (1927) who obtained similar results, but used no animal under 35 days of age. Such results are also consistent with findings in dogs (Stewart, 1921), rabbits (Taylor, Drury & Addis, 1923) and man (MacKay, 1932).

It is also clear from the present results that the renal concentrations of RNA and DNA are higher in new-born than in adult rats, while the RNA/DNA ratio in the cortex is lower in the former than in the latter. This agrees with findings by Priestley & Malt (1968) and Malt & Lemaitre (1969) in new-born and foetal mice. A decrease in the concentrations of RNA and DNA with increasing age, however, is not unique to the kidney: it has also been observed in liver and heart (Oliver, Ballard, Shield & Bentley, 1962; Baserga, Petersen & Estensen, 1966).

Of interest was the observation that the contralateral kidney of unilaterally nephrectomized new-born rats underwent compensatory hypertrophy, as in adult animals, and that the magnitude of hypertrophy was markedly greater in neonatal than in more mature rats (Fig. 2). As rats' kidneys are particularly immature at birth (Heller, 1947; McCance & Wilkinson, 1947; Dicker, 1952; Falk, 1955; Dicker & Shirley, 1971*a*), it seems surprising, in the light of renal functional inadequacy, that new-born rats tolerated the operation at all. But since unilaterally nephrectomized neonatal rats grew as well as did sham operated or control animals, it may be that the protein anabolism accompanying growth relieved the kidneys of the necessity of excreting nitrogenous end products (McCance & Widdowson, 1957), a factor which may go some way towards explaining the survival of neonates after unilateral nephrectomy.

The present results have shown that after unilateral nephrectomy of new-born rats there was, as in adults, a rise in the RNA/DNA ratio of the remaining kidney, and that, again as in adults, this rise was limited to the cortex. The increase, however, was only about half as great as that in adults (Dicker & Shirley, 1971*b*), suggesting that in new-born rats the degree of cellular hypertrophy is less than that in adults. Since, on the other hand, the increase in renal *mass* is *greater* in new-born animals, a reasonable conclusion would be that a major contribution to compensatory growth in young animals comes from cellular hyperplasia. This may not seem so surprising when it is remembered that there is still an active nephrogenic zone in the kidneys of 5-day-old rats; one would possibly expect cells which are still actively dividing to be more easily stimulated to greater mitotic activity than could the cells of the adult's kidney, in which basal mitotic activity is low.

The rate of oxygen uptake by the cortex of the remaining kidney of unilaterally nephrectomized rats was enhanced for up to 3 weeks after the operation, and, when expressed per cell, was still high after 65 days. This rise, of a similar magnitude to that found in adult rats (Dicker & Shirley, 1971*b*), but lasting much longer, agrees with observations of mitochondrial proliferation (Johnson & Amendola, 1969) and increased activity of Na-K-activated ATPase (Katz & Epstein, 1967; Fanestil, 1968) observed in the renal cortex after unilateral nephrectomy. The absence of any change in the Q_{O_2} of the medulla after unilateral nephrectomy agrees with observations in adults (Dicker & Shirley, 1971*b*), and is consistent with the relatively small compensatory response occurring in this region (Oliver, 1944–45; Dicker & Shirley, 1971*b*).

It would thus appear that the main difference between the compensatory renal hypertrophy of neonatal and adult rats is a greater rate of renal growth in the former, due very likely to an enhanced rate of hyperplasia. This agrees with Brasel's (1972) results.

One of us (D.G.S.) was in receipt of an M.R.C. training grant.

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