ON THE COMPENSATORY HYPERTROPHY OF THE ISCHEMIZED KIDNEYS

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In 1959 one of the authors of this article [1] developed a method of producing a standard degree of stenosis in the arteries of rats in chronic experiments by means of a stenotizing spiral. Experimental test of this method showed that after the application of a spiral with a spire diameter of 0.3-0.35 mm upon one of the renal arteries the corresponding kidney underwent atrophy, and the contralateral – intact – kidney underwent hypertrophy. If, however, a spiral with a spire diameter of 0.3 - 0.35 mm was pulled over one of the renal arteries and stenosis of the artery in the second kidney was simultaneously produced by the application of another spiral with a spire diameter of 0.26 mm, the first kidney (in which the stenotic artery had a diameter of 0.3-0.35 mm) did not undergo atrophy, but hypertrophy.

It was the aim of the present investigation to confirm this observation experimentally.

EXPERIMENTAL METHOD

We carried out 3 series of experiments. In the first series, stenosis of the renal artery was produced in one kidney; in the second series, stenosis – of different degree – was produced in both renal arteries; and in the third series, stenosis was produced in the renal artery of a kidney which had earlier undergone hypertrophy. In all experiments, the stenotizing spiral was left on the arteries until the end of the animals' life.

White rats of both sexes and of coinciding weight (between 158 g and 375 g) were used for the experiments. The following parameters were used to judge the degree of renal hypertrophy and atrophy: the size of the kidneys, the size of the glomeruli and of the tubules, and the general histological picture (in sections stained with hematoxylin-eosin, picrofuchsin and Sudan III). The size of the glomeruli and of the tubules in the proximal part of the nephron was measured by means of an eyepiece-micrometer. The size of the glomeruli was measured within the limits of the renal corpuscles, summing up their total size along the greater diameter, and the size of the tubules was measured at the basal membrane. In each section the diameter of 30 glomeruli and of 30 contorted tubules of the first order was measured in 3 different parts of the kidney (in the upper, middle and lower third of the organ). In each kidney the measurements were carried out in 3 sections after which the average values were calculated.

To assess the functional state of the kidneys the non-protein nitrogen level was estimated in the blood of arbitrarily selected animals.

EXPERIMENTAL RESULTS

I. Experiments Involving the Production of Stenosis in One Renal Artery.

Stenosis in one of the renal arteries was produced in 18 rats: in 11 rats with the aid of a spiral with a spire diameter of 0.3 - 0.35 mm, and in 7 rats by means of a spiral with a spire diameter of 0.4 - 0.46 mm.

If the arteries were narrowed by means of a spiral with a spire diameter of 0.4 - 0.46 mm, atrophy of moderate degree developed within 45 days in the corresponding kidney, without compensatory hypertrophy of the contralateral kidney.

If the arteries were narrowed by means of a spiral with a spire diameter of 0.3 - 0.35 mm, marked atrophy of the ischemized kidney and compensatory hypertrophy of the intact kidney could be observed, beginning from the 12th- 14th day. At later stages the signs of atrophy and sclerosis in the ischemic kidney became more marked and

by the 200th-300th day the organ was completely replaced by fibrous, frequently petrified tissue. In these cases the hypertrophy of the intact kidney reached a high degree. The atrophy of the ischemic kidney became manifest in the diminished size of the glomeruli and the contorted tubules.

The average size of the kidney, the artery of which had been rendered stenotic throughout the duration of the experiment (12-300 days), reached 12. 6 × 8 × 5 mm; as compared to 18 × 10 × 8 mm in the controled animals. (All control values described in this paper were obtained on 10 intact rats). The average size of the contralateral kidney reached 19.3 × 12.3 × 9.3 mm.

The diameter of the glomeruli in the ischemic kidneys decreased to 60 - 65 μ, compared to 68 - 76 μ in the control animals (i.e. a decrease of 8 - 11 μ) and the diameter of the tubules reached 23 - 28 μ instead of 30 - 38 μ

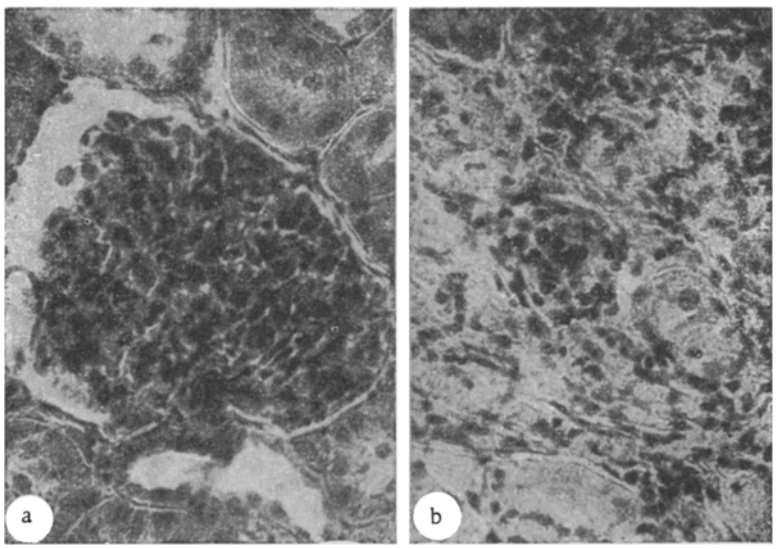

Fig. 1. Simultaneous experimental stenosis of both renal arteries. 44th day of the experiment. On the left: a hypertrophic glomerulus and tubules (stenosis of the renal artery with a diameter of 0.35 mm); on the right: atrophic glomerulus and tubules; fibrosis of the kidney (stenosis of the renal artery with a diameter of 0.26 mm).

(i.e. a decrease of 7 - 10μ). In the contralateral kidney the glomeruli increased to a diameter of 80 - 125 μ (on the average to 99.6μ) and the contorted tubules of the first order reached a diameter of 36 - 45 μ (on the average 40μ).

Investigation of the non-protein nitrogen in the blood of arbitrarily selected animals revealed in 4 rats with a stenotized renal artery, and in 6 control rats that the non-protein nitrogen levels are very similar in both groups in the experimental animals the level varied between 21 and 36 mg% (on the average 29 mg%) and in the control rats between 21 and 46 mg% (on the average 37 mg%).

If one generalized the results of the first series of experiments one comes to the conclusion that experimental stenosis of the main artery in one kidney leads to the atrophy of the kidney and to the hypertrophy of the contralateral kidney. The nitrogen excretion by the kidneys remains on the whole unimpaired.

II. Experiments Involving Simultaneous Stenosis – of Different Degree – in both Renal Arteries

In the second series of experiments simultaneous stenosis of both renal arteries was produced in 17 rats. The artery of one of the kidneys was narrowed with the aid of a spiral similar to that used in the first series of experiments with a spire diameter of 0.3 - 0.35 mm and the artery of the other – contralateral – kidney was narrowed by means of a spiral with a smaller spire diameter equal to 0.26 - 0.28 mm. In various groups between one third and two thirds of all animals used for the experiments survived. The highest mortality could be observed within the first 10 - 14 days of the experiments.

In the second series of experiments, in which the observation was continued for up to 230 days, the kidneys, the renal arteries of which had been rendered stenotic to a diameter of 0.3 - 0.35 mm, did not undergo atrophy – in contrast to the experiments of the first series – but became hypertrophic. The fact of hypertrophy could in these cases be confirmed by the increase in size.

In this series of experiments the average size of the kidneys, in which the renal artery had been rendered stenotic to a diameter of 0.3 - 0.35 mm, reached 20 × 11.8 × 2.8 mm as compared to 12.6 × 28 × 5 mm in the first series of experiments and 18 × 10 × 8 mm in the control group.

Microscopical investigation of the kidneys, the arteries of which had been rendered stenotic to a diameter of 0.3 - 0.35 mm, revealed that the increase in the size of the organ had been caused by an increase in the size of the glomeruli and the tubules (Fig. 1, 2). In these kidneys the diameter of the glomeruli varied in the course of the experiment between 91 and 105μ, (on the average 99.6μ) compared to 68 - 76μ in the control rats (on the average 72μ); the diameter of the tubules increased to 43 - 48μ (average 45μ) compared to the average diameter of the tubules in the control animals (34μ).

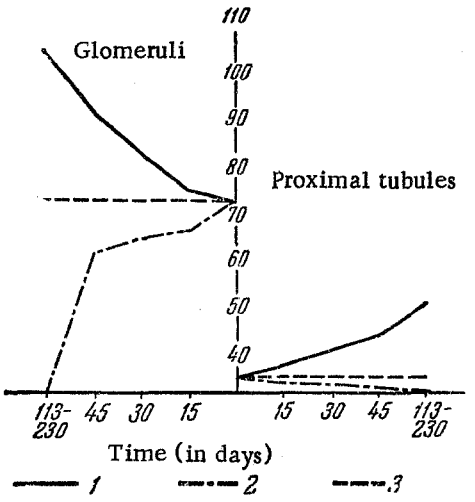

Fig. 2. Experimental stenosis produced simultaneously in both renal arteries. The pattern of changes in the size of the glomeruli and the tubules (the average diameters are given in μ). 1) Kidney in which the renal artery had been rendered stenotic to a diameter of 0.3 - 0.35 mm; 2) kidney in which the renal artery had been rendered stenotic to a diameter of 0.26 mm; 3) kidney of a control rat.

Estimation of the blood non-protein nitrogen in 4 arbitrarily selected rats of the second series showed that the non-protein nitrogen level varies within the same range (25 - 45 mg %, on the average 39 mg %) as in the normal control rats (21 - 46 mg %, on the average 37 mg %).

The results of the second series of experiments show that one and the same degree of stenosis of the nutrient artery (0.3 - 0.35 mm) can lead to both atrophy and hypertrophy, depending on the requirements of the body, as determined by the state of the other kidney. A hypertrophic kidney with a stenotic artery – just as a hypertrophic kidney with an intact artery – is able to sustain a state of compensation for a relatively long period, as shown by the fact that the non-protein nitrogen is kept on a level very close to the normal level observed in the control of animals and by the long life which lasted up to 230 days. At later stages of the experiment necrotic nephrosis develops in the hypertrophic kidneys with stenotic arteries (second series) just as in the hypertrophic kidneys with intact arteries (first series).

III. Experiments Involving the Production of Stenosis in the Renal Arteries of Kidneys Which Had Earlier Undergone Hypertrophy

In the third series of experiments we studied the influence of experimental stenosis produced in the renal artery upon the hypertrophic kidney in 15 rats. To produce hypertrophy in one of the kidneys a spiral with a spire diameter of 0.24 - 0.26 mm was pulled over the renal artery of the contralateral kidney. After 27 - 60 days, the ischemic kidney became hypertrophic. At this stage a stenotizing spiral with a spire diameter of 0.3 - 0.35 mm was pulled over the artery of the hypertrophic kidney, which spiral had produced atrophy of the kidney in the first series of experiments.

Notwithstanding stenosis of the renal artery the hypertrophic kidney did not undergo atrophy, but as a rule, the hypertrophy became more intensive. The size of the hypertrophic kidneys at the moment the stenosis was produced in the renal artery varied between 17.5 × 10 × 8 mm and 19.5 × 10 × 8 mm (average values 18.5 × 10 × 8.5 mm); 69 days after the second operation – at the moment of the animals' death – the kidneys showed a further increase in size reaching 20 × 13 × 10 mm and up to 23 × 12 × 11 mm (average 20.8 × 12.7 × 10.4 mm).

Histological investigation revealed that the continued increase in size, observed in the previously hypertrophic kidneys after their renal artery had been rendered stenotic, was caused by an increase in the size of the glomeruli and the tubules. The diameter of the tubules increased – compared to the normal values (control group) – on the

average by 22μ, and the diameter of the tubules, by 18μ; in this, just as in the preceding series of experiments, no disorders in the nitrogen excretion could be observed.

The animals used for the third series of experiments survived on the average for 125 days. The decompensation of the hypertrophic kidneys, the arteries of which had been rendered stenotic, usually occurred under symptoms of increasing necrotic nephrosis, similar to what had been observed in the hypertrophic kidneys in the first two series of experiments.

The results of the third series of experiments show that – unlike the intact kidney – the hypertrophic kidney does not respond with atrophy to the same degree of stenosis, produced in the nutrient artery, but that, as a rule, the hypertrophic process goes on.

Our findings coincide with the results of Koletsky [3] who showed that a temporary complete ligation (for 2-3 hours) in one of the renal arteries in rats leads to the atrophy of the corresponding kidney and does not prevent its subsequent hypertrophy if the contralateral intact kidney is later removed.

Our findings are also consistent with the experiments of Hinman [2] who showed that a temporary complete ligation (for 2-3 weeks) of the ureter leads to hydronephrosis and atrophy of the corresponding kidney but does not prevent its hypertrophy after the removal of the intact contralateral kidney.

Summing up our experimental results we are able to establish the following main principle which governs the structural and functional changes in ischemic kidneys: one and the same degree of stenosis in the renal artery may lead to different functional and structural changes (atrophy or hypertrophy) depending on the requirements of the body, as determined by the state of the other kidney.

We have reason to believe that the principle governing the structural and functional changes of ischemic kidneys, established by us, is not of special character but represents a generally valid biological law, which law, after the accumulation of further factual material, might well prove valid for other ischemic tissue structures.

SUMMARY

Three series of experiments were staged on 60 white rats: I – stenosing of the artery of one kidney; II – a simultaneous but differing-in-degree constriction of the arteries of both kidneys; III – stenosing of the arteries of formerly hypertrophied kidneys. Histological and laboratory-clinical investigation was carried out. Besides the size of the kidneys, glomeruli and tubules were determined to assess the degree of hypertrophy and atrophy. It is elicited that with the same degree of renal artery stenosis the structure and the function of the first kidney may vary (atrophy – hypertrophy) depending on the body requirements in connection with the condition of the second kidney.

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