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EFFECT OF ACUTE ANOXIA ON SERUM RENIN AND ERYTHROPOIETIN ACTIVITY IN RATS

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The kidneys have not only an excretory function, but they also play the role of an endocrine organ, producing biologically active substances and hormones such as renin, kinins, prostaglandins, and erythropoietin. The stimulus for renin secretion is a change in the blood supply to the kidneys and, in particular, reduction of the blood flow through the renal arteries, with a fall of the perfusion pressure [3]. However, changes in the hemodynamics of the kidney also affect the biogenesis of erythropoietin, a hormone which regulates erythropoiesis [7]. Thus a fall in the blood flow in the renal tissue may lead to simultaneous stimulation of these two biologically active substances.

This paper describes a comparative study of the serum renin and erythropoietin concentrations in rats with an "endocrine" kidney and changes in the activity of each of these compounds after exposure to a specific erythropoietic stimulus, namely anoxia.

EXPERIMENTAL METHOD

Inbred rats weighing 100-120 g and (CBA × C57Bl)F_1 mice were used. There were three main series of experiments: I) normal animals; II) rats on the 7th day of occlusion of the abdominal aorta; III) animals undergoing mock operations at the same time. The animals in each series were additionally exposed to anoxia for 4 h. The experimental model of an "endocrine" kidney was obtained by the method in [14]. The aorta of the anesthetized rats was ligated with Kapron on a stylet 0.34 mm in diameter, thus constricting it to the same size as the stylet. Adequacy of the model was verified by ligation of a ureter in some of the rats, followed by observing the presence or absence of hydronephrosis. The second control test was a histologic investigation during which the state of the parenchyma of the renal cortex and medulla was studied. On the basis of these two tests a technique for producing the "endocrine" kidney was developed. If a contralateral "intact" kidney was present, the rats did not develop renal failure. In some rats the right "intact" kidney was removed on the 7th day of occlusion of the aorta through a dorsal incision. During the next 4 h these animals were kept either under ordinary atmospheric conditions or in a hypobaric chamber. To exclude any effect of operative stress, a mock operation was performed on some of the animals, resembling the operation to obtain an "endocrine" kidney but without ligation of the aorta. Hypobaric anoxia, induced by exposure of the animals in a hypobaric chamber to

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TABLE 1. Changes in Serum Renin Activity of Rats Subjected to Acute Anoxia (exposure 4 h)

Series of experiments	Experimental conditions	Number of animals	Renin activity, mg/ml/h	p
I	Normal rats	6	31,4±2,51	
II	Normal rats + anoxia	6	36,6±3,5	>0,1
III	Rats of control group undergoing mock operation	5	33,9±4,4	>0,1
IV	Mock operation + anoxia	5	34,4±2,26	>0,1
V	Rats with "endocrine" kidney on 7th day after operation	7	51,0±4,4	<0,05
VI	Rats with "endocrine" kidney + anoxia	7	50,1±1,8	>0,1

Legend. Results of series V differ significantly from those of control (III) series of experiments.

TABLE 2. Changes in Serum Erythropoietin Titer in Rats after Operation and Exposure in Hypobaric Chamber (4 h)

Experimental conditions	Percent incorporation of ^{59}Fe into erythrocytes of postanoxic mice	Number of mice taken for testing	Percent of control value	p
Normal rats	0,77±0,1	5		
Rats undergoing mock operation	1,3±0,12	5	169	<0,001
Rats on 7th day of occlusion of aorta	1,92±0,2	8	250	<0,001
Rats with "endocrine" kidney alone	1,66±0,18	8	210	<0,001
Normal rats + anoxia	3,2±0,2	8	400	<0,001
Rats on 7th day after operation + anoxia	4,1±0,8	8	530	<0,001
Rats with "endocrine" kidney alone + anoxia	3,34±0,4	14	433	<0,001

a pressure of 47.2 kPa for 4 h, was used as the erythropoietic stimulus. Plasma erythropoietic activity was determined by measuring incorporation of radioactive iron into the erythrocytes of the postanoxic mice by Cotes's method in the modification in [2]. The radioactive samples were counted in a scintillation counter with RFT-20026 calculator. Renin activity was determined by radioimmunoassay using SB-Ren-2 kits (France–Italy). The radioactivity of the samples was counted on an "Ultragamma" scintillation counter.

EXPERIMENTAL RESULTS

Occlusion of the abdominal aorta in the rats and reduction of the blood flow in the left "endocrine" kidney led to an increase in the serum renin concentration of the animals. For instance, on the 7th day after the operation the serum renin concentration of these rats was 63% higher than in normal animals, and 54% higher than in rats of the control group undergoing a mock operation (Table 1).

There is evidence that constriction of the abdominal aorta or unilateral constriction of a renal artery causes a decrease in renin secretion in the contralateral "intact" kidney, with a simultaneous increase in the renin concentration in the "endocrine" kidney [5, 12]. It is evidently the "endocrine" kidney which creates the raised renin background.

Exposure for 4 h in a hypobaric pressure chamber caused virtually no change in the level of renin secretion either in rats undergoing the real or mock operation or in normal animals (Table 1). A similar effect of acute anoxia on renin activity is found in man [8]. The authors cited showed that exposure to anoxia for 1 h does not change the level of renin activity in subjects tested. A short stay in a hypobaric chamber evidently has no marked action on renin production in the kidneys.

The study of erythropoietin formation in the experimental groups described above showed that the erythropoietin titer on the 7th day of aortic occlusion was raised to 250% of the control value (Table 2). To identify which of the two kidneys in the rats subjected to the operation was the source of production of large quantities of erythropoietin, the contralateral "intact" kidney was removed. It was found that a high serum erythropoietin activity was maintained in the rats with a residual "endocrine" kidney (Table 2), evidence that this kidney is involved in erythropoietin synthesis.

Exposure of rats undergoing the operation to subsequent anoxia led to a further rise in the erythropoietin level, to an equal degree whether both kidneys or only the "endocrine" kidney remained (Table 2). During construction of the abdominal aorta it is thus evidently the "endocrine" kidney and not the contralateral "intact" kidney that is responsible for increased production of erythropoietin and renin.

Disturbance of the hemodynamics, even in one kidney alone, is thus a general stimulus which triggers the mechanisms of synthesis and activation of products of the endocrine function of the kidney. A common feature to the biogenesis of erythropoietin and renin is the activating action of prostaglandins (PG). For instance, the role of PGE_1 and PGE_2 in an increase in the activity of renin [4, 9] and erythropoietin [1, 13] has been demonstrated, whereas inhibition of PG synthesis by indomethacin led to a fall in the activity of these hormones in the blood serum [10, 11]. It has accordingly been suggested that common mechanisms of the biogenesis of these two biologically active compounds may exist and that a single structural element synthesizes both renin and erythropoietin. However, the data now obtained on an "endocrine" kidney model contradict this view. Animals with an "endocrine" kidney after exposure in the pressure chamber responded by a raised serum erythropoietin level but without any change in renin activity, although its initial level was higher than in the control. A similar response to acute anoxia was shown also by control animals with a normal initial level of these hormones: in response to a 4-h period of anoxia the serum erythropoietin titer rose whereas renin activity remained at the control level. Clear dissociation between the activity of these two hormones also was found by other investigators in experiments with salt loading and administration of cobalt [6], and on that basis it was suggested that erythropoietin synthesis and renin synthesis are stimulated separately. Hypobaric anoxia is a selective stimulus for erythropoietin biogenesis, with no marked influence on renin formation. Despite the close interconnection of these two biologically active substances in the kidney, each of them has its own specific mechanism of stimulation, and on that basis it can be concluded that the mechanisms of biogenesis of these two renal hormones differ.

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