CONCENTRATION OF RENIN IN THE KIDNEYS IN EXPERIMENTAL HYPERTENSION

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The role of the renal-humoral factor in the development of hypertension has not yet been finally explained. Very great importance is attached to this factor in the onset and consolidation of the hypertensive state [7, 8, 10, 11].

Advances in biochemistry and improvements in experimental technique have led to a re-examination of previous ideas in relation to the renin-hypertensin system [2,3]. The study of the biochemical nature of hypertensin has been followed by discovery of its structure, and subsequently by its synthesis [15, 17, 18]. A detailed study has been made of the biochemical nature of the enzymic action of renin on the serum α_2-globulins [9, 14]. More and more facts have accumulated incompatible with the fundamental assumptions of the humoral theory.

The accumulation of renin in the kidneys and blood in chronic hypertension has not been confirmed by many investigations [12, 13, 16, 19]. Experimental researches devoted to the study of pressor substances have been conducted mainly on the renal form of hypertension, i.e., in conditions when in the early stages the blood supply to the kidneys was deliberately modified, which could affect the metabolism of the organ and be reflected in the renin concentration.

A matter of great interest is the study of the content of pressor substances (especially renin) in the period of development of experimental reflexogenic hypertension, when the marked increase in the arterial pressure is unrelated to direct interference with the renal circulation. Little information on this aspect of the problem is to be found in the literature [4, 6].

We have studied the concentration of renin in the kidneys at intervals during the development of chronic reflexogenic hypertension in rabbits, and also in acute experiments for periods of 1.5 h after removal of the pressure receptors of the arch of the aorta and the carotid sinuses.

EXPERIMENTAL METHOD

The renin in the kidneys was estimated quantitatively by means of biological tests after the preliminary conversion of the renin into hypertensin by the technique developed at the Institute of Therapy of the USSR Academy of Medical Sciences [1, 5]. The animals in which the pressor substances in the kidneys were investigated after measurement of the arterial pressure were sacrificed by air embolism. The renin was immediately isolated from the renal cortex by the method we have indicated. As hypertensinogen we used globulin isolated from normal horse serum.

EXPERIMENTAL RESULTS

Repeated investigations of samples after incubation of different quantities of a saline extract (1:10) of the cortex of normal kidneys (renin) and different quantities of globulin (hypertensinogen) gave the following results. Renin (the least quantity), obtained from the renal cortex of rabbits aged from 6 to 12 months and used to obtain hypertensin in a concentration of 0.05-0.1 ml/kg body weight of the test animal with hypertensinogen in an amount of 2.5-5.0 ml/kg body weight, gave rise to the formation of hypertensin, which raised the arterial pressure of most of the rabbits (each weighing 2.0-2.2 kg) by 20 mm. We selected this quantity of hypertensin as our standard unit of measurement.

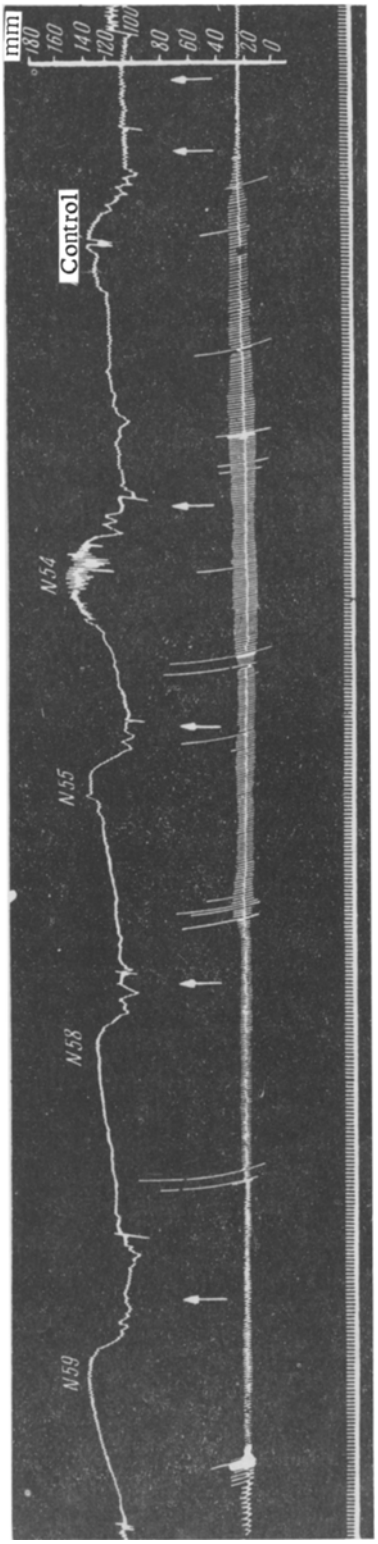

Fig. 1. Reaction of the arterial pressure of a rabbit to injection of hypertensin obtained from the kidneys of rabbits with reflexogenic hypertension. Significance of the curves (from above, down): arterial pressure, respiration, time marker (1 sec). The arrow indicates the beginning of injection of the preparation.

In all the experiments the investigations of the kidneys of animals with experimental hypertension were accompanied by control investigations of the kidneys of normal animals. Hypertensin obtained from the kidneys of the experimental and control animals was tested in rabbits weighing 2.0-2.2 kg (rarely, 2.4-2.5 kg). The hypertensin, diluted with physiological saline, was injected into the jugular vein. We used the kidneys of 51 rabbits with chronic reflexogenic hypertension at various periods of development (17 animals 4-21 days after the second operation, 26 animals 2-6 months later, and 8 animals 10-16 months later) and the kidneys of 30 normal animals.

Several series of investigations were carried out: a group of animals with hypertension of the same duration and a control animal with a normal arterial pressure were sacrificed on the same day. The reaction to isolate hypertensin from a given quantity of kidney tissue was performed, and the biological test was carried out on the same animal. Experiments of this type conducted on animals with hypertension lasting 3 months are illustrated by the kymogram (Fig. 1).

In order to generalize the results obtained by the biological test, we analyzed them in accordance with the formula suggested by Braun-Menendez:

$$U = \left(\frac{d}{t}\right)^2,$$

where U is the number of units of hypertensin in the test solution; d the increase in arterial pressure resulting from injection of the test solution; and t the increase in arterial pressure following injection of the control hypertensin solution.

In Fig. 2 we show the content of hypertensin (in conventional units in relation to the controls) obtained from the reaction between hypertensinogen and the renin isolated from a given quantity of renal cortex in the group of normal animals and the animals with hypertension at different stages of development.

According to our findings, the activity of the hypertensin obtained by the method we have described from a given volume of the renal cortex varied in normal animals between 0.8 and 1.4 conventional units; in animals with hypertension lasting from 4 days to 3 weeks – between 0.4 and 1.4 conventional units; and in animals with hypertension lasting from 2 to 6 months – from 0.2 to 2.6 conventional units. The least activity was shown by the tissue from animals in the late stages of development of a hypertensive state (0.16 to 1.0 unit).

It will be clear from these findings that in the early periods of development of chronic hypertension (4th-21st day) no increase in the content of pressor substances was observed; on the contrary, in cases in which the arterial pressure was significantly raised above the initial level, the pressor activity of the cortex was decreased.

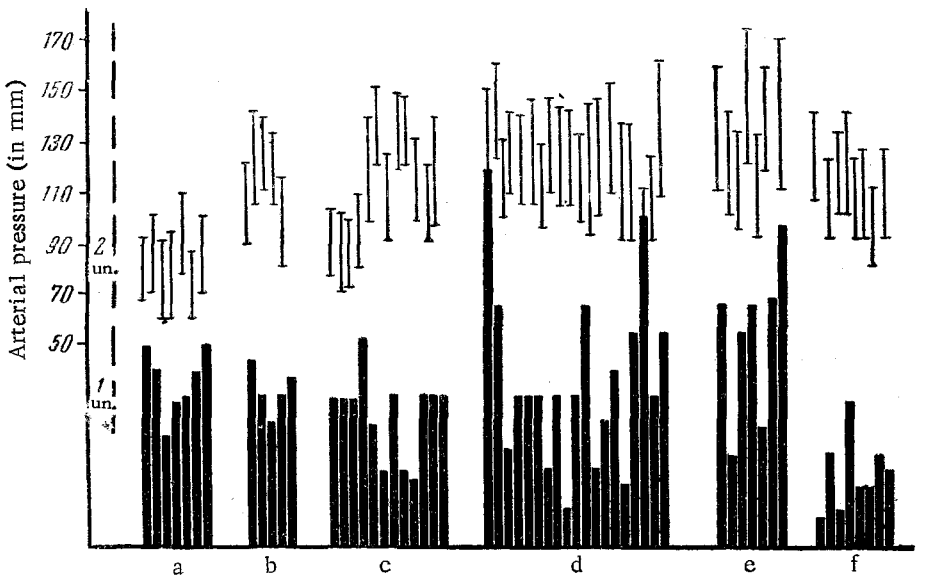

Fig. 2. Amount of hypertensin (in conventional units) obtained from a given volume of the cortex of kidneys from normal and hypertensive rabbits and the level of the arterial pressure of the animals investigated: a) normal rabbits; b) rabbits with hypertension lasting 4 days; c) 2-3 weeks; d) 2-4 months; e) 6 months; f) 10-16 months.

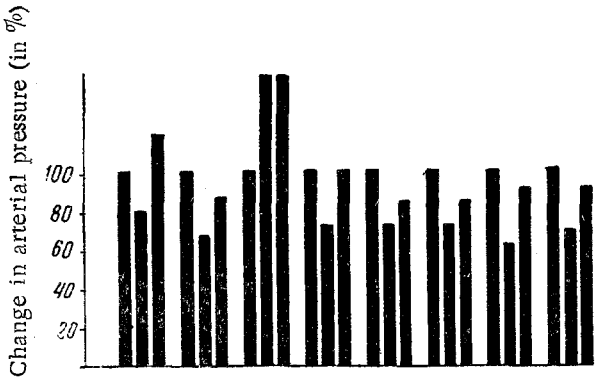

Fig. 3. Change in the level of the arterial pressure of rabbits after injection of hypertensin obtained from the same volume of the renal cortex of rabbits before and after removal of the pressure receptors of the arch of the aorta and carotid sinuses (elevation of the arterial pressure after injection of hypertensin obtained from the renal cortex before removal of the pressure receptors taken as 100%). First columns, before operation; second, 20-25 min after operation; third, 90 min after operation.

The impression was gained that at this period the raised arterial pressure depresses the renin-forming function of the kidneys, which may to some extent be regarded as the compensatory reaction of the granular cells of the juxtaglomerular apparatus (in which it is considered that renin formation takes place) to the rapid changes in the level of the arterial pressure after removal of the pressor receptors.

In the period of establishment of experimental hypertension (from 2 to 6 months) considerable variations in the activity of the renal cortex were observed. A high renin content by comparison with normal animals was observed in less than half the experimental animals. It may be supposed that in the period of established hypertension the disturbance of the neurotrophic influences of the central nervous apparatuses leads to changes in the metabolism of the kidneys and to an inadequate reaction of the juxtaglomerular apparatus to the altered vascular tone; a specific type of dysfunction in the production of protein (renin) is observed, related to the regulation of the level of the arterial

pressure. In the late periods of development of hypertension, when the hypertension has, in fact, disappeared, some lowering of the activity of the cortex was observed by comparison with the controls. This may have been due to the activation at this period of mechanisms concerned in the destruction of renin, or possibly to sclerotic changes in the kidneys.

In a series of acute experiments we investigated the activity of the pressor substance which we were studying during the 90 min after removal of the pressure receptors. In an anesthetized animal, after measurement of the arterial pressure the abdomen was opened and tissue was taken from the renal cortex (80-100 mg) by means of an electrocautery. Subsequently the pressure receptors of the arch of the aorta and carotid sinus were removed bilaterally, and after intervals of 10-25 and 80-90 min samples of the renal cortex were again taken. Renin was isolated from all the samples, and after conversion to hypertensin, was tested biologically in a rabbit. Investigations in this manner were carried out on 8 animals. Removal of the pressure receptors of the arch of the aorta and carotid sinuses in all the animals caused an increase of 23-45 mm in the arterial pressure. Observations were made of the changes in the content of pressor substance before and after removal of the pressure receptors, demonstrating that 20-25 min after this operation the pressor activity of the cortex fell in 7 of the 8 animals, and rose again after 80-90 min, approaching the original state in certain rabbits (Fig. 3).

These experiments showed conclusively that removal of the pressure receptors, accompanied by an increase in the arterial pressure, leads to a rapid fall in the pressor activity of the renal cortex, followed 80-90 min after the operation by an increase in pressor activity.

SUMMARY

A study was made of the renin content in the kidneys during the development of chronic reflexogenic hypertension in rabbits and in acute experiments for 1.5 hours after section of pressure receptors of the aortic arch and carotid sinuses. The quantitative content of renin in the kidneys was determined by means of biological tests with preliminary conversion of renin into hypertensin. In a chronic course of reflexogenic hypertension no rise in renin content was noted in the kidneys at early periods of development. At the period of stable hypertension (2 to 6 months) a considerable fluctuation of the renal cortex activity was observed in the animals with hypertension. At late periods of hypertension some reduction of the renin content was noted in the kidneys. Removal of pressure receptors of the aortic arch and carotid sinuses in acute experiments changed the content of pressor substances.

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