MECHANISM OF RENAL INVOLVEMENT IN THE PATHOGENESIS OF EXPERIMENTAL NEUROGENIC HYPERTENSION

COMMUNICATION II. CORRELATION OF RENAL CIRCULATION AND RENAL RENIN CONTENT IN EXPERIMENTAL NEUROGENIC HYPERTENSION AND FOLLOWING DENERVATION OF THE KIDNEYS

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According to widely held views the cause directly responsible for increased production of renin during the development of hypertension is progressive renal ischemia. This view is based on the fact that hypertension caused by constriction of renal arteries (so-called "Goldblatt hypertension") is accompanied by enhanced renin secretion and a rise in renin content of the kidneys [15, 19].

V. N. Chernigovsky and collaborators developed a new concept in a series of investigations [4, 5, 6, 8, 9] which postulates that in the courseof development of neurogenic hypertension, formation of renin in the kidneys is stimulated by the nervous system independently of changes in renal blood flow.

The present work was concerned with direct elucidation of the significance and the role of renal ischemia in the mechanism of renal pressor factor involvement and more especially of the renin system in experimental neurogenic hypertension.

With this aim in view a study was made of renal circulation both during "inclusion" of the renal pressor factor in experimental neurogenic hypertension and during its "exclusion" by means of denervation of the kidneys.

EXPERIMENTAL METHODS

Experiments were carried out on rabbits weighing 1.8 to 2.3 kg.

Induction of hypertension, measurements of arterial blood pressure, denervation of the kidneys and determination of renin content of the kidneys were performed in ways similar to those described in previous papers by one of the authors [4, 5].

Two criteria were used in determining the state of renal circulation: renal blood flow and the so-called filtration fraction, whose value represents the ratio of filtration to plasma flow and gives an idea of the relative tonus of afferent and efferent blood vessels.

Renal blood flow was determined by Diodrast clearance coefficient, glomerular filtration by endogenous creatinine clearance coefficient. Clearance coefficients for these substances, according to modern data, represent most nearly the state of the respective renal functions in the rabbit [22]. For the sake of greater precision the investigation was carried out under conditions of practically constant blood levels of Diodrast. This was achieved by continuous drip, maintained at a constant rate. Sterile Diodrast solution, 80 mg% in physiologic solution, was

used for the injections.

The animal was immobilized on a table in the supine position. A needle connected in the usual manner with a vessel containing Diodrast solution was inserted into the pinna vein and the drip started. The rate of 1-1.5 ml per minute was maintained by means of a screw clamp situated above the dropper.

Preliminary administration of Diodrast designed to create the necessary blood level was continued for 30 minutes. At the beginning of this period the femoral artery was exposed and ligated.

In each experiment determination of renal function was, as a rule, performed over three periods of time, each 13 to 35 minutes in duration. The urine excreted during each of these periods was collected by catheter; the bladder was then washed out with 50-60 ml of warm water which was aspirated by a syringe. Blood was taken from the femoral artery in amounts of 5-6 ml, in one part of the experiments by means of a cannula, in another – by gravity.

Chemical estimations of blood and urine Diodrast were carried out by the Alpert [11] method; creatinine was estimated by one of the modifications of Folin's method [17].

Clearance coefficients were calculated in the standard way. The described procedure involved fairly considerable (for rabbits) withdrawals of blood, which made it necessary to obtain evidence excluding changes of blood pressure during the investigation itself. For this purpose repeated measurements of arterial pressure were taken on 3 healthy rabbits throughout the period during which clearance coefficients were being determined; observations of arterial pressure were carried out during each experiment on hypertensive rabbits. No significant alterations of blood pressure were discovered.

EXPERIMENTAL RESULTS

The first and fundamental series of experiments was devoted to a study of correlations between renal circulation and renal renin content in experimental neurogenic hypertension.

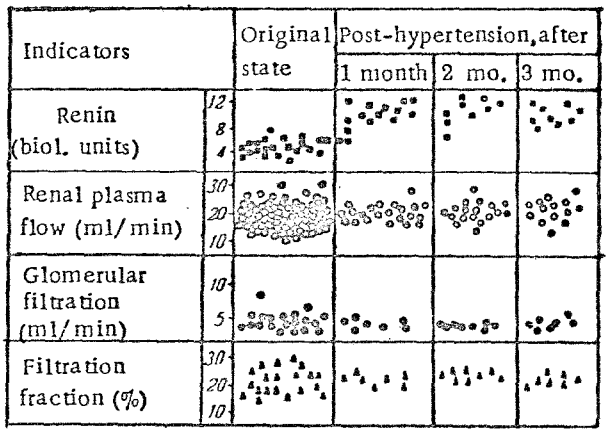

Fig. 1. Indicators of renal circulation and renal renin content at the onset of experimental "inhibitory" neurogenic hypertension.

Observations on indicators of renal functions were carried out over a period of 3 months following development of hypertension.

Renal blood flow was determined in 72 rabbits with normal pressures and in 22 of these it was again determined after onset of hypertension.

Glomerular filtration and, correspondingly, filtration fraction were determined in 20 healthy rabbits and traced in 8 of them during developed hypertension. Renal renin content was estimated in 22 rabbits with normal pressures and in 33 rabbits with experimental neurogenic hypertension.

As revealed by investigations, renal plasma flow (blood flow), glomerular filtration and filtration fraction in the normal showed very considerable differences (Fig. 1). Therefore, in order to evaluate these indicators after the development of hypertension it was necessary to determine the degree of their variability from day to day in one and the same normal animal. Results of 4 experiments staged for this purpose demonstrated pronounced individual fluctuations in the values which characterize renal function. Renal plasma flow and glomerular filtration in the same rabbit varied in different directions in the course of 1-1$^1/_2$ months up to 60-85% with respect to the original level. It was therefore considered to be preferable to compare the results obtained on hypertensive rabbits with all the data relating to the normal in order to achieve a more correct elucidation of changes in renal functions in hypertension.

The values for indicators of renal functions, as well as the wide range of their fluctuations obtained in the present investigation agree with data in the literature [13, 16, 18]. It seems significant also that the values for renal blood flow correspond to the results of direct blood flow determinations (Rein method) [21, 23].

During experimental neurogenic hypertension the values characterizing renal blood flow, glomerular filtration and filtration fraction did not leave the limits of the original figures (Fig. 1). Consequently no changes in renal circulation could be detected during 3 months following the onset of experimental neurogenic hypertension. At the same time, as can be seen from Fig. 1, the renin content of the kidneys showed marked changes during the same stages of the development of hypertension. As early as the first month there was considerable increase in renin content; this remained essentially constant in the following two months. Similar results were obtained by V. N. Chikvaidze [10].

Thus in the initial period of the development of neurogenic hypertension the increase in renal renin occurred in the absence of changes in renal circulation.

These data confirm the hypothesis postulated earlier by the present authors concerning the trophic nervous influences exerted on the kidney and maintaining the development of neurogenic hypertension.

R. Bing and later A. I. Vyshatina [12, 2] also did not observe any changes in renal blood flow and other renal functions in the first few months following development of experimental neurogenic hypertension. Vyshatina suggests that this indicates absence of renal pressor mechanism involvement in the pathogenesis of the early stages of neurogenic hypertension.

In the light of the results reported above this suggestion must be rejected as erroneous.

The second series of experiments consisted of a study of the effect of renal denervation on the correlation of renal circulation and renal renin content.

Indicators of excretory renal function were studied in 12 rabbits with normal blood pressure, and renin content in 22, both after denervation of the kidneys. Similar determinations were carried out on 14 hypertensive rabbits following renal denervation.

As in the first series of experiments the data obtained after denervation of the kidneys were compared with all the data characterizing the orginal state of renal function.

Denervation of the kidneys led to similar dynamics of renal function indicators and renin content in the normal and hypertensive rabbits (Fig. 2 and 3). In the first postoperative days, during which blood pressure and renin content of the kidneys remained at the original level, indicators of renal circulation showed a sharp drop.

It must be supposed that these changes depend on the marked stimulation of afferent and efferent renal nerves caused by their section and subsequent painting with phenol. True exclusion of the kidneys from the system of nervous influences supervened later. During this period a fall of blood pressure and renal renin content were observed, while indicators of renal circulation became stabilized at the original level.

Thus the drop in blood pressure caused by denervation of the kidneys and the almost complete disappearance of renin occur without appreciable changes in renal circulation.

The absence of any effect of severance of renal neural connections on the excretory function of normal kidneys has already been noted previously [1, 3, 23].

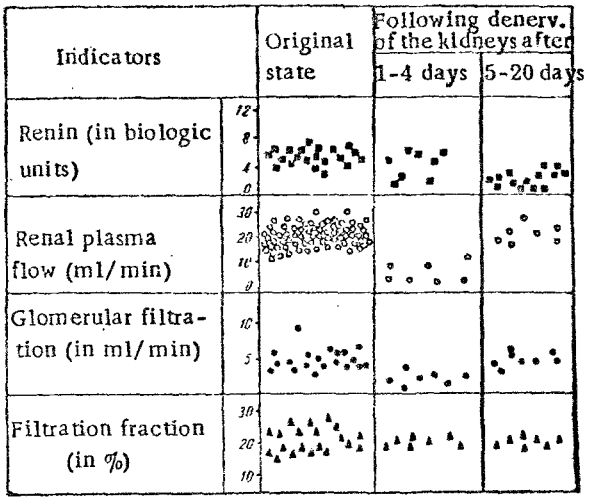

Fig. 2. Indicators of renal circulation and renin content following denervation of the kidneys in healthy rabbits.

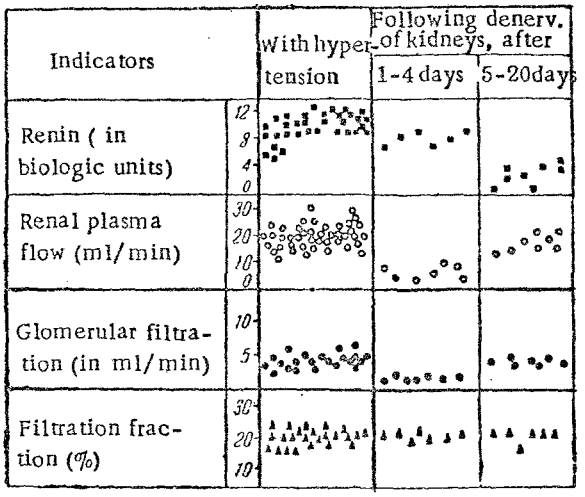

Fig. 3. Indicators of renal circulation and renin content following denervation of the kidneys in hypertensive rabbits.

It is important to remark in this connection that the workers [7, 14] who first discovered the depressor effect of denervation of the kidneys in experimental hypertension associated it with cessation of strong vasoconstricting influences. The present data refute such a hypothesis for the mechanism of cessation of hypertension following denervation of the kidneys. Exlusion of the renal pressor factor takes place independently from the state of renal circulation.

The results of the present work reject the significance of renal ischemia in the mechanism of neurogenic renal involvement, the renin system in particular, in the pathogenesis of experimental neurogenic hypertension, and thus confirm the point of view developed by V. N. Chernigovsky and his collaborators.

SUMMARY

Renin content of the kidneys and renal blood flow were determined in rabbits during the course of hypertension, induced by section of the pressor regulator nerves and after renal denervation, which abolishes neurogenic hypertension. The experiments revealed that trophic nervous influences on the kidneys, necessary for the induction of neurogenic hypertension, result in an excessive production of renin, which takes place in the absence of renal ischemia.

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