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EFFECT OF CALCITONIN ON MECHANISMS OF URINE FORMATION AND SODIUM EXCRETION IN HORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS

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An important role in the genesis of hypertensive states, especially spontaneous hypertension of rats, is ascribed to disturbances of calcium metabolism [7, 9, 11]. Accordingly, attention has recently been paid to the study of the possible role of calcium-regulating hormones in these disturbances. Considering the importance of the kidneys in physiological regulation of blood pressure and calcium metabolism, studies of the effects of calcium-regulating hormones on renal activity must be of great interest. Calcitonin has been studied the least in this respect. Effects of calcitonin on excretion of electrolytes (Ca, K, Na, P) have been described in fair detail [2, 5, 8], whereas the effect of the hormone on the mechanisms of urine formation has not yet been fully explained, for there have been reports both of its diuretic [1, 5] and of its antidiuretic effects [6, 11]. However, these data were obtained on normotensive animals, and no description of the study of renal effects of calcitonin in hypertensive animals could be found in the accessible literature.

The aim of this investigation was to study the effects of calcitonin on the excretory function of the kidneys under conditions of spontaneous diuresis in normotensive (NR) and spontaneously hypertensive (SHR) rats.

EXPERIMENTAL METHOD

Experiments were carried out on 80 SHR of the Okamoto-Aoki line and 90 NR of the Wistar line, aged 24-26 weeks; all the rats were males weighing 200-250 g and were kept on a permanent diet of food and water. Animals of the experimental groups were given an injection of a Soviet preparation of hog calcitonin (calcitrin) in a dose of 0.6 U/100 g body weight, whereas the control rats received the same volume of physiological saline. To collect the urine, the animals were kept for 6 h in metabolism cages. The volume of urine excreted was measured, glomerular filtration was determined relative to endogenous creatinine, and tubular reabsorption of water was then calculated. The Na concentration in the urine was studied by flame photometry, and

*Deceased.

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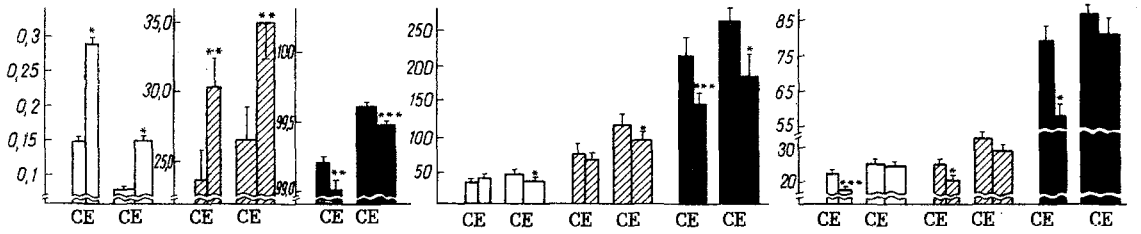

Fig. 1 Fig. 2 Fig. 3

Fig. 1. Effects of calcitonin on volume and processes of urine formation in normotensive and spontaneously hypertensive rats. Unshaded columns — volume of diuresis (ml/h/100 g); obliquely shaded columns — rate of glomerular filtration (ml/h/100 g); black columns — level of tubular reabsorption of water (per cent). Here and in Figs. 2 and 3, narrow columns indicate normotensive rats; wide columns — spontaneously hypertensive rats. C) control animals, E) experimental rats after receiving 0.6 U calcitrin. Differences from control group: $*p < 0.05$, $**p < 0.01$ or $p < 0.02$, $***p < 0.001$ or $p < 0.002$.

Fig. 2. Effect of calcitonin on urea concentration in layers of renal tissue. Here and in Fig. 3: unshaded columns — cortex, obliquely shaded outer medulla; black — renal papilla.

Fig. 3. Effect of calcitonin on sodium concentration in layers of renal tissue.

the sodium excretion was calculated. In blood collected after decapitation, renin activity and the aldosterone concentration were determined by radioimmunoassay, using kits from "Oris" (France) and the vasopressin level was measured with kits from "Bühlmann" (Switzerland). The Na and urea concentrations (the latter by Gasanov's method) were determined in the layers of renal tissue (cortex, outer medulla, and renal papilla).

EXPERIMENTAL RESULTS

Injection of calcitonin in the above dose into NR led to a significant increase in the volume of urine excreted (by 93%), on account of a decrease in tubular reabsorption and a considerable increase in glomerular filtration (by 28%; Fig. 1).

Injection of calcitonin into SHR caused a similar response of an increase in the volume of urine excreted (by 87%), but from a lower initial level, on account of a significant decrease in the tubular reabsorption of water and an increase in glomerular filtration (by 31%).

However, in the hypertensive animals the reduction of water reabsorption was less marked, evidently due to the higher initial level. In SHR, the lower background value of urine formation also depended on this factor: 53% of its volume in NR.

To clarify the mechanisms of this diuretic effect, the results of a study of plasma renin activity and vasopressin level were analyzed. The results showed that renin activity was not significantly changed under the influence of calcitonin either in NR or in SHR (from 9.14 ± 0.86 to 10.76 ± 0.866, $p > 0.01$, and from 10.87 ± 1.4 to 8.2 ± 0.639 ng/ml/h, $p > 0.01$, respectively).

The vasopressin level, however, was significantly lowered in the hypertensive animals, while remaining virtually unchanged in NR (from 29.16 ± 2.13 to 23.17 ± 1.43, $p < 0.05$, and from 22.45 ± 1.12 to 26.35 ± 1.55 moles/liter, $p > 0.01$, respectively).

The effectiveness of working of the concentrating mechanism was assessed by studying the concentrations of urea and sodium in the layers of the kidneys. It was found (Fig. 2) that the concentration of urine in NR was significantly lowered under the influence of calcitonin in the renal papilla, and remained unchanged in the cortex and the outer part of the medulla. A decrease in the urea concentration was observed in all layers of the kidney in SHR.

The Na concentration (Fig. 3) in NR was significantly reduced in all layers of the kidney. In SHR, no changes in the Na concentration in the renal tissues were found under the influence of calcitonin.

It can be concluded from these results that the significant decrease in tubular reabsorption of water observed in the experimental normotensive rats was due to a decrease in osmolarity of the renal tissues on account of Na and urea and, correspondingly, on the efficiency of the concentrating mechanism when the plasma vasopressin level was unchanged.

Inhibition of tubular reabsorption of water in SHR was associated both with a decrease in osmolarity of the interstitial tissues of the kidney due to a decrease in the urea concentration accompanied by an unchanged Na level, and with a decrease in the plasma vasopressin concentration.

The results given above can be compared with the presence of the natriuretic effect of calcitonin in the experimental NR (from 21.7 ± 1.68 to 47.4 ± 4.71, $p < 0.001$) and its absence in SHR (from 19.6 ± 1.45 to 22.1 ± 2.32 μmoles/h/100 g, $p > 0.1$). In this case the initial plasma aldosterone level was higher in NR. In the experimental animals of both groups a significant fall of the hormone level was observed, but it was greater in NR (from 0.52 ± 0.03 to 0.15 ± 0.02, $p < 0.001$, in NR and from 0.36 ± 0.03 to 0.2 ± 0.04 nmoles/liter, $p < 0.02$, in SHR).

Comparison of the osmolarity of the layers of kidney tissue in the experimental animals revealed an initially higher Na and urea level in the SHR. One result of this may probably he the higher background values of tubular reabsorption and low value of volume of urine excreted by these animals.

Thus a distinguishing feature of the response of hypertensive rats to calcitonin is inhibition of water reabsorption due both to a fall of the vasopressin level and weakening of the effects of vasopressin associated with reduced osmolarity of the outer layers of the medulla and the renal papilla, due to a decrease in the urea concentration. The vasopressin level in NR was unchanged, but inhibition of reabsorption was evidently connected with the more marked decrease in osmolarity of the interstitial tissue, for besides urea, the Na concentration in the layers of the kidney also was reduced.

In SHR, according to our data, resistance was observed to the natriuretic effect of calcitonin, which we found in NR and which has been widely described in the literature in normotensive animals [4, 5, 8].

This kind of response of an increase in glomerular filtration in the animals of both experimental groups under the influence of calcitonin suggests a vasodilator effect of the hormone, and this is confirmed by lowering of the systemic arterial pressure found in the previous experiments [3]. Further evidence in support of this view is given by the decrease in osmolarity of the interstitial tissue due to a decrease in the urea concentration in the outer layer of the medulla and in the renal papilla, i.e., to realization of its so-called flushing effect.

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