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EX AEDIBVS ACADEMICIS IN CIVITATE VATICANA

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URINARY KININOGENASE AND RENAL HYPERTENSION

H.R. CROXATTO and M. SAN MARTIN

SVMMARIVM — Disceptat Auctor de activitate Kininogenaseos quae invenitur in urina et sanguine in relationem ad nimium arteriarum sanguinis pressum.

The specific physiological role of kininogenases (kallikreins) enzymatic system remains uncertain as yet. Kininogenase releases kinins which are potent vasodilator peptides. Their effect in the blood vessels is the reverse to that produced by angiotensins which are set free by renin. Angiotensin through aldosterone production by adrenal cortex promotes sodium reabsorption in the nephrons. By contrast kinins, such as bradykinin, induce in the kidney a strong natriuretic effect [1]. Kininogenase is present in the renal tissue and can be readily extracted by several procedures proposed to purify renin [2]. These results lead us to study as to whether kininogenase is involved in kidney functional impairment which promotes the

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raise of blood pressure and modify renin liberation by the kidneys.

Experiments were undertaken to measure kininogenase activity (k.a.) in the urine and in the renal tissue of rats submitted to a kidney manipulation which is followed by renal hypertension. Here are reported the k.a. determinations in the urine of normotensive and hypertensive rats.

Hypertension was induced in 20 male, adult rats (Sprague-Dowley strain) using the GROLLMAN procedure [3]. In a first stage a figure-in-8-ligature was made in one kidney and a week later the other one was removed. A group of 10 uninephrectomized rats was used as control. Blood pressure was measured in the rat tail by the microphone technique [4] at weekly intervals beginning 10 days after extirpation. Every week or fortnight the urine was collected by placing the animals in individual metabolic cages. In many experiments only the freshly voided urine was used for assays but in some cases the urine was collected for several hours in order to carry out purification procedures (dialysis, gel filtration). The k.a. was determined either in dialysed or non dialysed urine using two bioassays: the contraction of isolated rat uterus and the depressor effect on the blood pressure of an anesthetized rat. Previous experiments [5 and 6] have shown that urinary kininogenase has a direct oxytocic effect which is dose dependant and is correlated with the magnitude of its vasodepressor effect. An standard bradykinin solution was used to quantificate the k.a. This was expressed in ng of bradykinin which produce equivalent oxytocic effect per ml of urine.

In the fig. 1 are summarized the results obtained in four different determinations carried out on the 70, 75, 84 and 108 days after the kidney removal. The k.a. in the urine of rats bearing the figure in-8-ligature, are given separately according to the blood pressure at the moment of urine collection. The most conspicuous result is the highly significant decrease in the k.a. in the hypertensive rats. In this group 10 rats had

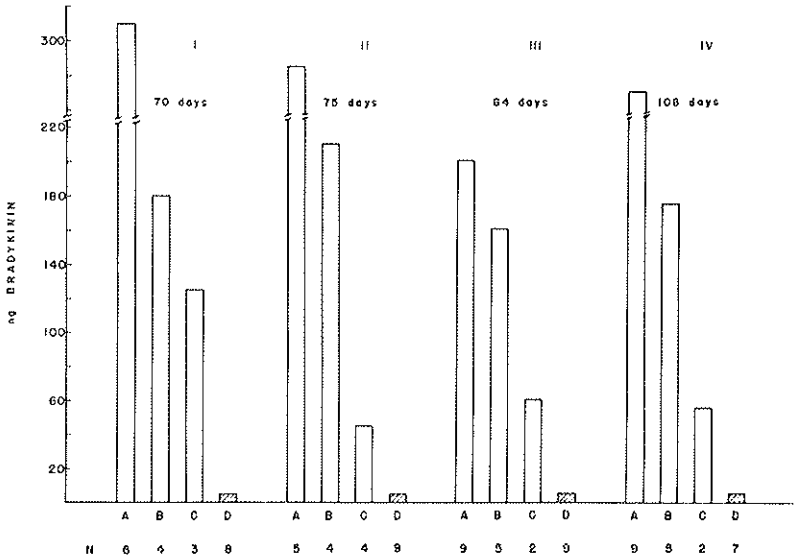

FIG. 1 — The columns represent means values of the kininogenase activity per ml of urine expressed in ng of bradykinin found in 4 groups of rats:
A. Uninephrectomized rats (normotensive).
B.C.D. Uninephrectomized and with figure-in-8-ligature in the remnant kidney. Blood pressure in the rats of these 3 groups were at the moment of testing: B, 120-130 mm; C, 140-150 mm and D, 160-220 mm Hg.
The lower row of ligures indicate the number of rats.
The figures in the upper part represent the days after the kidney removal, when the tests were performed.

$P < 0.001$ when D is compared to C, to B and to A.

In the last 3 assays the differences on k.a. among the four groups were highly significant. ($P = 0.01 — < 0.001$).

constantly high blood pressure (between 160-220 mm Hg) and the k.a. in the urine in all of them was less than 10 ng bradykinin. In the control uninephrectomized rats k.a. oscillated between 200-310 ng of bradykinin per ml. In a group of 5 rats having the figure-in-8-ligature which did not develop hypertension or had a transient elevation of the blood pressure, k.a. was significantly higher than that found in the hypertensive rats. In these animals which at the moment of the last assay

had practically normal blood pressure (120-130 mm Hg) a mean value of 175 ng of bradykinin per ml was found. This figure is about 65% the k.a. of the uninephrectomized control group. When the figure-in-8-ligature rats show a moderate o fluctuating blood pressure the k.a. is significantly lower than that recorded in the normotensive and very often fluctuates from one week to the other.

The date obtained using the uterus bioassay were confirmed by the vasodepressor test. Chronological studies disclosed that lower values of k.a. in the urine are found immediately after the kidney removal as compared to the normal. Later on k.a. decreases also when the operation is performed, however it diminishes even more if the animal becomes hypertensive. A striking fall in the k.a. persists until death ensues providing the rat keeps permanently a high blood pressure.

Although the experiments do not give evidence that k.a. in the urine is involved in the mechanism of arterial hypertension they show that an inverse correlation with the blood pressure exists, suggesting that k.a. reflects the kidney impairment which is responsible of the blood pressure elevation. It is possible to speculate that the « protective » action of an intact renal tissue against hypertension can be related with kidney kininogenase activity.

Research performed at the Instituto de Fisiología de la Universidad Católica de Chile, Santiago.

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