RENIN – ANGIOTENSIN – ALDOSTERONE SYSTEM IN RATS WITH NEUROGENIC STRESS

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In adult male rats moderate neurogenic stress was induced by crowding for periods of 1 and 7 days. The angiotensin I concentration and renin activity in the blood plasma and the aldosterone concentration in the peripheral blood and adrenal tissues were determined radioimmunologically. Crowding the rats for 1 day led to a considerably marked increase in the adrenal aldosterone concentration in the plasma. The aldosterone concentration in the blood and adrenals of the rats was lowered 7 days after the beginning of neurogenic stress but the renin activity and angiotensin I concentration in the peripheral blood plasma were raised. The causes of the dissociation observed in the renin–angiotensin–aldosterone system in response to neurogenic stress of varied duration are discussed.

KEY WORDS: stress, renin–angiotensin–aldosterone system.

The renin–angiotensin–aldosterone system plays an important role in the regulation of water and mineral homeostasis and of the blood pressure (BP), in the pathogenesis of some forms of arterial hypertension, edema, and other pathological states [2, 10]. This system is also known to possess negative feedback [4], which is exhibited in the event of a primary increase in aldosterone secretion, as in Conn's syndrome [9] for instance. The behavior of this system in certain stress situations, especially those of neurogenic nature, is an interesting problem which has not been sufficiently studied.

The effect of neurogenic stress on renin activity and on the angiotensin level in blood plasma and also on the aldosterone concentration in the blood and adrenals was investigated in rats.

EXPERIMENTAL METHOD

Male noninbred albino rats with a mean weight of 280 g were used. Neurogenic stress was induced by keeping the rats under crowded conditions when they had to "fight for living space" in order to obtain access to food and water, when their usual ecological relations were disturbed and, consequently, they were exposed to powerful psychogenic stimulation [11]. The animals of group 1 were kept under crowded conditions for 1 day, those of group 2 for 7 days, whereas the rats of group 3 were kept under ordinary conditions and acted as the control.

The animals were decapitated and the blood was collected into plastic tubes in the cold with the addition of EDTA solution (0.15 ml of the 6% solution to 10 ml blood). Plasma was obtained by centrifugation at 4°C and was frozen until required for determination of its renin activity and aldosterone concentration.

The adrenals were quickly removed from the rats, carefully freed from surrounding cellular tissue, and homogenized with 1 ml Krebs–Ringer solution.

The angiotensin I concentration and renin activity in the plasma were determined by a radioimmunological method based on the work of Cohen et al. [8], and using a kit of reagents (Cis, France), with ^{125}I-labeled angiotensin I. By means of this method the angiotensin concentration and renin activity can be determined in 0.05 ml of undialyzed plasma.

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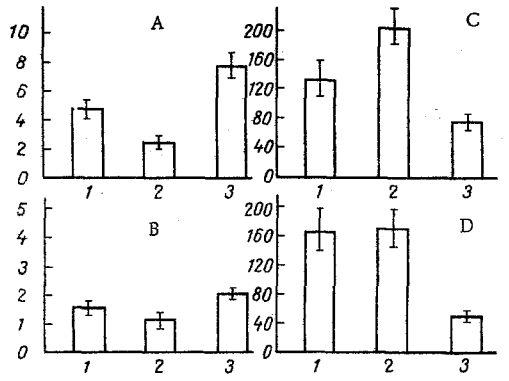

Fig. 1. Effect of neurogenic stress of different duration of renin–angiotensin–aldosterone system in rats: A) renin activity (in ng/ml/h); B) angiotensin I (in ng/ml); C) aldosterone in adrenals (in ng/2 adrenals); D) aldosterone in peripheral blood (in ng/100 ml). 1) Control, 2) after stress for 24 h, 3) after stress for 7 days.

The aldosterone content in the peripheral blood and adrenal tissue also was investigated by a radioimmunological method using a kit of reagents with ^{3}H-labeled aldosterone, obtained from the same firm, based on the method of Bayard et al. [5]. Not less than 1-1.5 ml plasma and 0.1 part of adrenal homogenate were used for one determination. Aldosterone was purified by thin-layer chromatography in a system of ether–benzene–acetone (25 : 15 : 10). These determinations of the blood aldosterone level in the rats may perhaps have given somewhat overestimated values because of the additional background remaining after chromatographic purification. When aldosterone was determined in the adrenals the effect of this factor was reduced virtually to zero because of the considerable dilution of the chromatographic residue.

Radioactivity was measured with the SL-30 (France) instrument with the use of the following scintillation fluid: PPO 4 g, POPOP 0.4 g, toluene 900 ml, Triton-X 100 ml.

EXPERIMENTAL RESULTS

The results are shown in Fig. 1. The angiotensin I concentration and, in particular, the renin activity in the blood were reduced 24 h after the beginning of stress in the rats, whereas on the seventh day these indices in the blood plasma were increased no less considerably. In the rats crowded for 24 h the aldosterone concentration in the adrenals was significantly increased. On the seventh day of crowding of the animals the aldosterone concentration in the adrenal tissue was sharply reduced (to 72.8 ± 3 ng), significantly so when calculated for two adrenals. However, the weight of the adrenals themselves was somewhat reduced in these rats (from 46.9 ± 3.25 to 41.2 ± 2.08 mg) and, consequently, the difference between the control and experiment, when calculated in ng/100 mg adrenal tissue was not significant. This indicates that the decrease in the aldosterone content in the whole adrenals was due, not to a decrease in activity of the enzymes concerned in aldosterone biosynthesis, but to a decrease in the quantity of secreting adrenal tissue.

Determination of the aldosterone concentration in the blood plasma of rats after different durations of crowding showed that 24 h after the beginning of stress the mean blood aldosterone concentration was unchanged, but on the seventh day it was considerably and significantly lowered.

Changes in the two principal components of the system (renin–angiotensin and aldosterone) under the influence of neurogenic stress for periods of 1 and 7 days were thus opposite in character. These findings were unexpected, for the following reasons: First, the renin–angiotensin–aldosterone system responds as a rule similarly (on the whole and by individual components) to various external stimuli such as changes in the salt regime, in the effective blood volume, and so on [3, 6, 10] and, second, the stimulating effect of the nervous system on the formation and secretion of renin and aldosterone (directly in the first case, indirectly through pituitary ACTH in the second) must now be taken as an established fact [15].

Admittedly most workers have studied the influence of the nervous system on renin and aldosterone secretion separately, and under different experimental conditions, and never simultaneously during exposure to the stress used in the present case.

It is logical to suppose that with this type of stress the increase in production and secretion of aldosterone and the subsequent sodium retention and increased intravascular volume develops sooner, as a result of which renin secretion is inhibited by a feedback mechanism. The fact that under these conditions activation of the sympathetic impulse flow to the kidneys could not increase renin secretion is further evidence of its less important (although quite definitely proven) effect on the activity of the juxtaglomerular apparatus of the kidneys than that of changes in the water and salt balance [15].

The unchanged aldosterone concentration in the peripheral blood despite a marked increase in its formation in the adrenals was evidently the result of its simultaneously increased utilization by the tissues and metabolism in the liver.

Since phasic changes in the secretion not only of glucocorticoids [1] but also, as the writers have shown, of mineralocorticoids take place in the course of chronic stress, this last fact (and, in particular, the fall in the blood aldosterone level on the seventh day of stress) not only abolishes the inhibitory effect of the negative feedback mechanisms on renin secretion, but also enables the stimulating action of the sympathetic nervous system on its secretion to be manifested under the conditions of neurogenic stress. As a result the renin secretion was increased 1 week after the beginning of stress at a time when the aldosterone concentration in the body (in the adrenals and blood) was reduced.

This type of dissociation between changes in the renin–angiotensin and aldosterone components has also been observed by other workers although, admittedly, under different experimental and clinical conditions [7, 12, 14].

The sharp dissociation in the changes in aldosterone concentration, on the one hand, and in the renin–angiotensin levels on the other hand, is known to be observed in Conn's syndrome [9] and in other forms of primary hyperaldosteronism, and also in the condition known as low-renin hypertension [13].

LITERATURE CITED

1. A. I. Barklaya, Probl. Éndokrinol., No. 12, 75 (1971).
2. Kh. M. Markov, The Pathophysiology of Arterial Hypertension [in Russian], Sofia (1970).
3. Kh. M. Markov, V. V. Bankova, and V. G. Pinelis, Pat. Fiziol., No. 6, 39 (1971).
4. M. G. Polyak, in: Aldosterone and Water–Salt Homeostasis [in Russian], Novosibirsk (1968), p. 123.
5. F. Bayard, I. Z. Beitins, A. Kowarski, et al., J. Clin. Endocrinol., 31, 1 (1970).
6. I. R. Blair-West, P. P. Coghan, et al., Am. J. Physiol., 287, 1409 (1973).
7. P. R. Boulter, R. F. Spark, and R. A. Arky, J. Clin. Endocrinol., 38, 248 (1974).
8. E.L. Cohen, C. E. Grim, J. W. Conn, et al., J. Lab. Invest., 50, 119 (1971).
9. J. W. Conn, R. F. Knopf, and R. M. Nesbit, Am. J. Surg., 107, 159 (1964).
10. J. O. Davis, I. T. Higgins, and J. Urquhart, in: Aldosterone, New York (1962), p. 175.
11. J. P. Henry, P. M. Stephens, and G. A. Santisteban, Circulat. Res., 36, 156 (1975).
12. A. M. Michelakis and R. Horton, Circulat. Res., 26, Suppl. 1, 1 (1970).
13. R. F. Spark, New Engl. J. Med., 287, 343 (1972).
14. H. Tsukiyama, K. Otsuka, S. Kyuno, et al., Jap. Circulat. J., 37, 1265 (1973).
15. A. I. Vander and R. Miller, Am. J. Physiol., 209, 537 (1964).