THE RENAL HUMORAL PRESSOR MECHANISM IN MAN.

III. THE HYPERTENSINASE CONTENT OF PLASMA OF CONTROL SUBJECTS AND OF PATIENTS WITH HYPERTENSION AND OTHER DISEASES[1]

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The pressor substance, hypertensin, formed by the action of the renal enzyme, renin, on plasma globulin, is easily destroyed by extracts of red blood cells as well as of kidney, intestine, and other tissues. Some authors (1) have called the hypertensin-destroying substance hypertensinase and consider it to be enzymatic in action. A relatively small amount of hypertensinase can be demonstrated also in normal, nonhemolyzed plasma. Methods of assay, as well as values for the hypertensinase in the plasma of normal, hypertensive, and nephrectomized dogs, have previously been published (2) and no difference was found from the normal in experimental renal hypertension. In the present series of experiments, the hypertensinase content of human plasma has been determined in control subjects and in patients with hypertension and other diseases.

METHODS

Hypertensinase was measured in human plasma, as previously described for dog plasma (2). Blood was drawn from the anticubital vein into 3.8 per cent sodium citrate. The amount of hemolysis in the plasma, as determined by benzidine, was never more than that of a 1:5000 dilution of packed red cells. Two or 3 samples (usually between 1 and 3 ml.) of each human plasma were incubated at pH 7.3 for 2 hours with 1 dog unit (1, 4) of hypertensin, after which the reaction was stopped either by alcohol or by heating at pH 4. Hypertensin without plasma was incubated as a control. The amount of hypertensin which was not destroyed by the hypertensinase of the plasma was determined by assay on cats (3). A unit of hypertensinase has been defined (5) as the amount which, in a volume of 10 ml. and containing 1 dog unit of hypertensin, destroys 0.5 dog unit of hypertensin in 4 hours at a temperature of 37° C. The results in the present paper have been converted to dog units of hypertensinase by means of a chart previously published (2). It was necessary to test the tubes promptly as hypertensin disappeared with prolonged standing. Because of the possibility of variations in the results at different times due to biological testing, normal and hypertensive plasmas were paired as often as possible.

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RESULTS

Hypertensinase content of normal human plasma. The hypertensinase contents of the plasmas of 10 subjects with normal blood pressure ranged from 1.1 to 1.8 dog units of hypertensinase per ml. of plasma (Table I). Each figure in the table represents the average of several samples tested. The values are slightly lower than similar determinations for dog plasma (2) which ranged between 1.6 and 3.9 dog units of hypertensinase per ml.

Hypertensinase content of plasma of patients with hypertension and other diseases. Results are summarized in Table I. The hypertensinase content of plasma of 16 patients with hypertension was the same as that of the normal control group by the methods used. In 6 patients with uremia, 4 of whom had hypertension and 2 normal blood pressures, hypertensinase values were normal. Normal titers were likewise found in the plasma of 2 patients with Addison's disease, which was well controlled with desoxycorticosterone and salt, and of 3 patients with disease of the liver, 2 of whom had marked hepatic insufficiency.

DISCUSSION

It has been suggested that hypertension may be due simply to a deficiency of a renal factor without the implication of a renal pressor substance or a balance between "anti-pressor" and "pressor" substances (6, 7). It is theoretically

TABLE I

The concentration of hypertensinase in the plasma of normal human subjects and of patients with arterial hypertension

Case	Blood pressure	Hypertensin destroyed in 2 hours	Units of hypertensinase	Diagnosis
	mm. Hg	*dog units per ml. plasma*		
		Normal		
1	130/70	0.50	1.5	
2	116/74	0.30	1.1	
3	115/84	0.38	1.3	Inactive pulmonary tuberculosis, mixed psychoneurosis
4	112/80	0.38	1.3	
5	110/75	0.42	1.4	Chronic inflammation of the genital organs
6	108/70	0.62	1.8	
7	106/72	0.50	1.6	
8	101/64	0.42	1.4	
9		0.40	1.4	
10		0.58	1.7	
		Hypertensive		
11	285/150	0.42	1.4	Chronic glomerular nephritis, uremia
12	240/162	0.35	1.2	Malignant hypertension
13	220/180	0.50	1.5	Malignant hypertension, hydronephrosis
14	214/110	0.30	1.1	Malignant hypertension, uremia
15	210/124	0.52	1.6	Hypertension, cerebral thrombosis
16	195/100	0.45	1.4	Hypertension, early cardiac insufficiency, adenoma of thyroid (nontoxic), generalized arteriosclerosis
17	192/113	0.55	1.7	Essential hypertension
18	190/115	0.38	1.3	Chronic pyelonephritis, diabetes mellitus
19	180/140	0.40	1.3	Hypertension
20	180/130	0.55	1.7	Essential hypertension
21	180/120	0.25	1.0	Essential hypertension
22	180/100	0.42	1.6	Hypertension, diabetes mellitus, hemorrhage into brain from arteriosclerosis
23	178/116	0.45	1.5	Chronic glomerular nephritis with nephrotic syndrome, uremia
24	164/126	0.40	1.3	Hydronephrosis and hydroureter, uremia
25	152/90	0.40	1.3	Preeclampsia
26	150/90	0.25	1.0	Active pulmonary tuberculosis, Addison's disease (treated), anemia
		Miscellaneous		
27	145/80	0.48	1.5	Hepatomegaly, hypertensive cardiovascular disease
28	126/60	0.33	1.2	Portal cirrhosis
29	125/75	0.37	1.3	Carcinoma of the urethra, uremia (fever)
30	108/40	0.35	1.2	Bronchopneumonia, acute nephritis, uremia
31	100/66	0.58	1.8	Laennec's cirrhosis, pulmonary tuberculosis
32	72/54	0.47	1.5	Hypoadrenalism (treated)

possible that the missing renal factor might be hypertensinase. Measurements of the hypertensinase content of human renal venous blood after clamping of the renal artery (8) have shown no significant differences from the normal. By the methods reported in the present paper, it is apparent that the amount of hypertensinase in human plasma is the same in hypertensive as in normal patients and that a lack of hypertensinase in plasma is not directly related to the presence of human hypertension.

The exact method of destruction of hypertensin by hypertensinase (1, 5) is not known, since the nature of the chemical reaction has not been studied in detail. Hypertensin is easily oxidized by potassium permanganate and hydrogen peroxide (9). It is inactivated by extracts of practically all tissues, especially intestine and kidney (5, 10, 11), and has been reported to be destroyed by various enzymes, including pepsin (1, 12, 17), amine oxidase, tyrosinase (11), amine polypeptidase, papain (12), trypsin (13, 17), chymotrypsin (17), and carboxypeptidase (17). Some authors (11, 14) have suggested that hypertensin is destroyed either by deamination or by destruction of a phenolic nucleus. They have reported that kidney extracts which destroy hypertensin have both amino peptidase and carboxypeptidase activity. Others (10) have found that renal deaminase which destroys certain pressor amines differed from the hypertensin-destroying substance in renal extracts. Hypertensinase has not been demonstrated to be an enzyme, although the influence of pH,

concentration, and temperature on its activity (5) would make it seem highly probable. There is probably more than one so-called hypertensinase. Hypertensinase from plasma and red blood cells, as well as that from muscle, liver, and intestine, has an optimum pH of approximately 7.5 or 8 (1, 5, 14), whereas that from kidneys is said to be 4.0 (15). Hypertensinase from serum is destroyed by incubation at a pH of 4 for 20 minutes at 37° C. (1, 16), whereas that from kidney is not (16). Few details are known of the origin, nature, and action of hypertensinase.

SUMMARY

1. The hypertensinase content of nonhemolyzed plasma of 10 normal subjects ranged from 1.1 to 1.8 dog units per ml. of plasma.

2. The hypertensinase content of the plasma of 16 patients with hypertension, 6 patients with nitrogen retention, 2 patients with Addison's disease, and 3 patients with hepatic disease did not differ from the normal.

3. It is concluded that there is no justification for considering that the blood pressure is high in human hypertension because of a deficiency of hypertensinase in plasma.

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