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Blood Pressure in Essential Hypertension Correlates with the Concentration of a Circulating Inhibitor of the Sodium Pump**

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Summary. The influence of serum from patients with essential hypertension on the sodium efflux rate constants of human lymphocytes and on the activity of isolated $(Na^+ + K^+)$-ATPase was investigated. The ouabain-sensitive sodium efflux rate constant was significantly decreased ($p < 0.001$) in the sera of 19 hypertensives ($1.92 \pm 0.11\ h^{-1}$) compared with the sera of 30 normotensives ($2.44 \pm 0.07\ h^{-1}$). The ouabain-insensitive sodium efflux was unaffected. These results corresponded with a significant difference ($p < 0.005$) of $(Na^+ + K^+)$-ATPase activity (1.03 ± 0.04 mU/ml and 0.079 ± 0.06 mU/ml), when an isolated $(Na^+ + K^+)$-ATPase was incubated with the sera of 22 normotensives or 18 hypertensives. Both the rate constant of ouabain-sensitive sodium efflux and the $(Na^+ + K^+)$-ATPase activity correlated significantly with the diastolic and systolic blood pressure ($p < 0.001$). These data, therefore, demonstrated the close relationship between essential hypertension and the concentration of a circulating inhibitor of the sodium pump.

Key words: Essential hypertension – Sodium pump – $(Na^+ + K^+)$-ATPase-circulating endogenous digitalis

Among the frequently discussed causes of essential hypertension is the impairment of sodium metabolism [2, 3, 21, 33, 35]. An elevation of intracellular sodium content has been attributed to an altered activity of the ouabain-sensitive sodium pump [10, 30–32, 34] and alterations in ouabain resistant sodium entry mechanisms as sodium-potassium cotransport or sodium-lithium countertransport [4, 5, 7, 11, 27, 34]. Recent reports have demonstrated that increased concentrations of circulating inhibitor(s) of the sodium pump in man [6, 14, 18, 24, 28] and in monkeys [13] are associated with essential hypertension. These inhibitors are claimed to have digitalis-like properties and are probably produced in the brain [1, 9, 17, 23]. Some of the evidence is based on rather small inhibitory effects [14] or on the very indirect assay for measuring the inhibition of $(Na^+ + K^+)$-ATPase: by a cytochemical technique via the stimulation of glucose-6-phosphate dehydrogenase [24].

The intention of this study was first to investigate the influence of sera from patients with essential hypertension on the sodium pump of human lymphocytes from healthy donors. Since the lymphocyte population is heterogeneous, the rate constants of sodium efflux were determined as parameters independent of cell size and quantity. Second, the effect of these sera on the activity of isolated $(Na^+ + K^+)$-activated ATPase (EC 3.6.1.37), the biochemical equivalent of the ouabain-sensitive sodium pump, was studied. A preliminary report of this work has been published elsewhere [22].

Materials and Methods

Patients and Controls

The rate constant of sodium efflux from human lymphocytes was determined in the sera of 19 hypertensive patients (11 males, 8 females) aged 20–74 years and of 30 normotensive subjects (21 males, 8 females) aged 23–49 years. The $(Na^+ + K^+)$-ATPase activity was measured in the sera of 34 hypertensives (21 males, 13 females) aged 19–73 years and 44 normotensives (30 males, 14 females) aged 23–50 years.

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Abbreviations: ATP = Adenosine triphosphate; EGTA = Ethyleneglycol bis(2-aminoethyl)-N,N,N′,N′-tetraacetic acid

All patients with essential hypertension who were hospitalized in our clinic, had blood pressure exceeding 140/90 mmHg. Blood pressure was measured wth a sphygmomanometer while patients were in a supine position and fasting. The blood pressure values were the means of repeated measurements made on two consecutive days. All patients had either been free from any medication for at least five days or had not been treated before the study. They were on a normal diet, i.e. without sodium restriction. Essential hypertension was diagnosed per exclusionem after a complete clinical and laboratory examination. None of the patients had signs of heart failure, renal disease, or endocrinopathy.

The normotensive controls were healthy volunteers from the staff who had blood pressure below 140/90 mmHg.

Sera from venous blood of all donors were frozen in 5-ml portions within half an hour after blood withdrawal, stored at −18° C, and thawed just prior to use.

Since sodium, potassium, and calcium may affect the sodium pump and $(Na^+ + K^+)$-ATPase activity [12], the serum concentrations of these ions were determined by flame photometry. The sera values of both the normotensives and hypertensives were within normal limits.

Determination of the Sodium Efflux Rate Constants of Human Lymphocytes

Human lymphocytes were isolated from the venous blood of normotensive controls by isopycnic centrifugation using the Ficoll-Paque technique [8, 16]. Siliconized glassware was used throughout the experiments. Immediately after blood withdrawal the heparinised blood was diluted with an equal volume of freshly prepared working solution consisting of 0.005 mM $CaCl_2$, 0.098 m*M* $MgCl_2$, 0.53 m*M* KCl, 126 m*M* NaCl, 0.01% glucose, and 14.5 m*M* Tris/HCl (pH 7.6). Each 30-ml portion of diluted blood was layered on 17 ml Ficoll-Paque (Deutsche Pharmacia GmbH, Freiburg, FRG) and centrifuged for 40 min at $400 \times g$ at 20° C. The lymphocyte layer was transferred to conical glass tubes and washed three times with working solution at room temperature. The final cell plug (about 4×10^7 lymphocytes) was suspended in 1.5 ml of serum from a normotensive or hypertensive donor supplemented with 4 µCi $^{22}NaCl$ (Amersham-Buchler GmbH, Braunschweig FRG). The lymphocytes were equilibrated for 90 min at 37 °C in a Dubnoff shaker. The tubes were then cooled in ice and the cells washed twice with ice-cold working solution. After removal of the supernatant, the $^{22}Na^+$-loaded lymphocytes were resuspended in 1.3 ml of the serum used for equilibration. To determine the ouabain-insensitive sodium efflux, 0.5 ml specimen was immediately added to 0.05 ml of a 5×10^{-4} *M* ouabain solution. This final concentration of 5×10^{-5} *M* ouabain has proved to be sufficient for inhibiting the sodium pump of human lymphocytes [22]. Both assays were then incubated in a Dubnoff shaker at 37 °C. Sodium efflux was determined by filtering 0.1 ml aliquots of the cell suspension on membrane filters with 0.45 µm pore size (Schleicher & Schüll GmbH, Dassel FRG) at timed intervals. The residue was washed with ice-cold working solution and a scintillation counter was used to measure the radioactivity. The rate constants of the sodium efflux were calculated according to the method of Hilton and Patrick [19] from the regression lines of the natural logarithm of radioactivity plotted against time. The rate constant of ouabain-sensitive sodium efflux was obtained from the difference of the rate constants of total sodium efflux and ouabain-insensitive sodium efflux.

Determination of the $(Na^+ + K^+)$-ATPase Activity

$(Na^+ + K^+)$-ATPase from pig kidney with a specific activity of 10–12 U/mg was isolated according to the method of Jørgensen [20] and quantitated in a coupled optical assay [29]. One enzyme unit (U) of $(Na^+ + K^+)$-ATPase was defined as the amount of enzyme protein hydrolyzing 1 µmol ATP per min at 37° C. The effect of serum on $(Na^+ + K^+)$-ATPase activity was studied at various enzyme concentrations (25 mU, 1.3 mU, and 0.26 mU per ml test) by liberating radioactive P_i from [γ-^{32}P]ATP (Amersham Buchler GmbH, Braunschweig, FRG). The assays were carried out in a total volume of 500 µl, consisting of 450 µl serum, 10 µl diluted enzyme, and 40 µl of a mixture composed of 1.5 µmol [γ-^{32}P]ATP (specific radioactivity 10^6 cpm/µmol), 2.15 µmol $MgCl_2$, 2.98 µmol KCl, and 1.25 µmol EGTA. To determine ouabain-insensitive activity, controls also containing 0.05 µmol ouabain were run in parallel. The average serum electrolyte content was 140 m*M* Na^+, 4.5 m*M* K^+, 0.78 m*M* Mg^{2+}, and 2.5 m*M* Ca^{2+}; the assay conditions were as follows: Na^+ 126 m*M*, K^+ 10 m*M*, Mg^{2+} 5 m*M*, Ca^{2+} 2.25 m*M*, EGTA 2.5 m*M*, ATP 3 m*M*. In the controls, ouabain was 10^{-4} *M*. At an enzyme concentration of 25 mU/ml, there were additional controls without serum but with equivalent electrolyte concentrations in 50 m*M* imidazole-HCl (pH 7.4). All determinations were done in duplicate.

After starting the reaction by adding 10 µl enzyme dilution which contained 12.5, 0.75, or 0.13 mU in 10 m*M* imidazole-HCl (pH 7.4), the incubation was performed at 37 °C for 5 min at 25 mU/ml, for 60 min at 1.3 mU/ml, and for 300 min at 0.26 mU/ml. Under these conditions the ATP hydrolysis was linear with time. The reaction was terminated by adding 100 µl of the incubation mixture to 500 µl of 5% (w/v) trichloroacetic acid. Denaturated protein was removed by centrifugation and 400 µl of the clear supernatant were used to determine inorganic phosphate according to the method of Martin and Doty [25]. In brief, the aliquots were mixed with a 5% (w/v) ammonium molybdate solution in 15% H_2SO_4 (v/v); the resulting phospho ammonium molybdate complex was extracted into a 1:1 mixture of isobutanol and benzene. After drying the organic phase on Na_2SO_4, the radioactivity was counted.

To calculate the rate of ATP hydrolysis, the specific radioactivity of the used ATP was measured and the enzymatic activity calculated from $^{32}P_i$ liberation. The amount of $(Na^+ + K^+)$-ATPase is the difference between the total rate of ATP hydrolysis and that determined in the presence of 10^{-4} M ouabain.

Since the number of assays that could be performed by the above procedure was limited and the amount of $(Na^+ + K^+)$-ATPase was not identical at high dilutions, the measurements at 1.3 mU/ml were combined by calculating the percentage inhibition of $(Na^+ + K^+)$-ATPase as a function of diastolic blood pressure. A regression analysis of enzyme activity versus the diastolic blood pressure was performed. The resulting mean value of $(Na^+ + K^+)$-ATPase activity at a diastolic blood pressure of 60 mmHg was arbitrarily set at 100%; all measured activities were then converted to percent inhibition.

Statistical Evaluation

Results were expressed as means ±SEM. Linear regression analysis, regression coefficients (r), and standard deviations (σ) were calculated using FORTRAN BMDP6D 81 (bivariate (scatter) plots). For statistical analysis the two-tailed Student's t test and the F test were applied.

Results

As indicated in Table 1, the rate constants for total sodium efflux and ouabain-sensitive sodium efflux were significantly decreased in the sera of 19 hyper-

Table 1. Influence of serum on sodium efflux rate constants of human lymphocytes (numbers of subjects in parenthesis)

	Normotensives	Hypertensives	Difference (%)	Student's *t* test
Diastolic blood pressure (mmHg)	73.2 ±1.30 (30)	107.0 ±2.30 (19)	+42	$p<0.0001$
Systolic blood pressure (mmHg)	120.0 ±2.10 (30)	184.7 ±5.00 (19)	+42	$p<0.0001$
Rate constants of $^{22}Na^+$-efflux from lymphocytes without ouabain (h^{-1})	3.64 ±0.06 (30)	3.06 ±0.11 (19)	−18	$p<0.001$
With 5×10^{-5} *M* ouabain (h^{-1})	1.19 ±0.06 (30)	1.17 ±0.07 (19)	− 2	$p>0.5$
Ouabain-sensitive $^{22}Na^+$-transport (h^{-1})	2.44 ±0.07	1.92 ±0.01	−27	$p<0.001$

Table 2. Influence of serum on $(Na^+ + K^+)$-ATPase activity at various enzyme concentrations (numbers of subjects in parenthesis)

$(Na^+ + K^+)$-ATPase in test system (mU/ml)	$(Na^+ + K^+)$-ATPase activity refound (mU/ml)			Student's *t* test
	Normotensives	Hypertensives	Inhibition (%)	
24.60[a] ±1.2	21.62 ±0.44 (12)	19.73 ±0.65 (7)	8.7	$p<0.05$
1.30[b]	1.03 ±0.04 (22)	0.79 ±0.06 (18)	23.0	$p<0.005$
0.26[b]	0.165 ±0.016 (10)	0.091 ±0.025 (9)	45.0	$p<0.05$

[a] Determined in control assays without serum
[b] Determined in the coupled optical assay

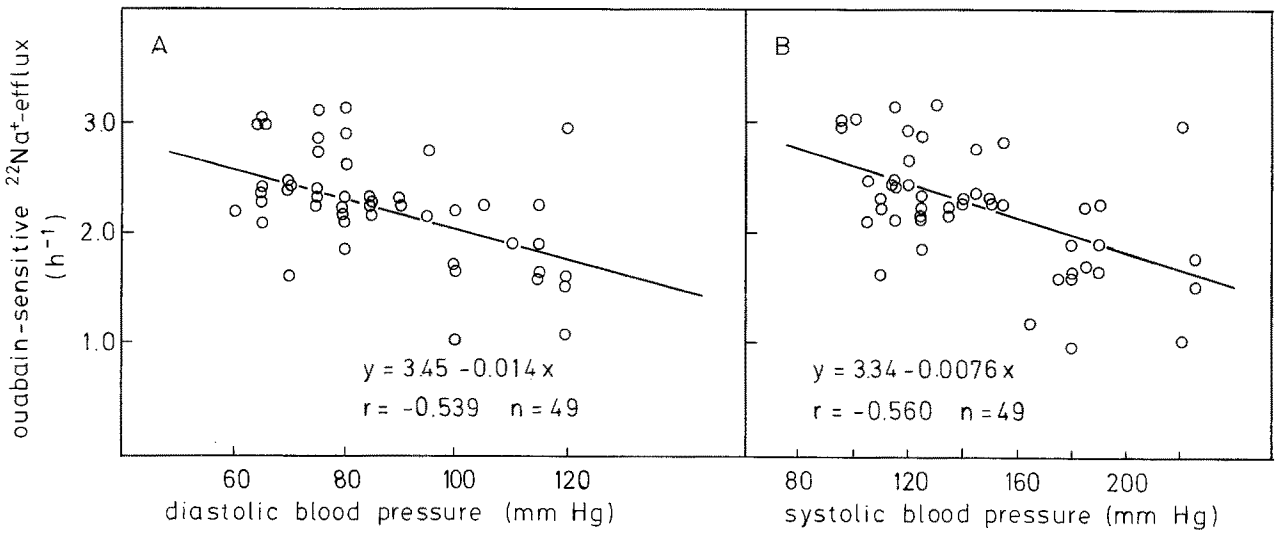

Fig. 1. Ouabain-sensitive ^{22}Na-efflux from preloaded human lymphocytes of healthy donors as a function of diastolic (*A*) and systolic (*B*) blood pressure

tensives compared with 30 normotensives ($p<0.001$). In contrast, the ouabain-insensitive sodium efflux rate constant was similar to that of controls. A 42% increase in diastolic blood pressure [73.2 mmHg (normotensives) to 107.0 mmHg (hypertensives)] was associated with a 27% reduction in the active (ouabain-sensitive) sodium transport. A significant negative correlation ($r=-0.54$; $p<0.001$) between the ouabain-sensitive sodium efflux rate constant (y) and the diastolic blood pressure (x) was found (Fig. 1 A). When systolic blood pressure values were used (Fig. 1 B), a similar correlation ($r=-0.56$; $p<0.001$) was found.

To study the effect of serum on the activity of isolated $(Na^+ + K^+)$-ATPase, the sera of 18 hypertensives (mean blood pressure 178±2.9/104±2.1 mmHg) and 22 normotensives (mean blood pressure 122±2.4/74±1.7 mmHg) were compared at an enzyme concentration of 1.3 mU/ml (Table 2). There was a highly significant difference of $(Na^+ + K^+)$-ATPase activity between the two groups ($p<0.005$), and a significant

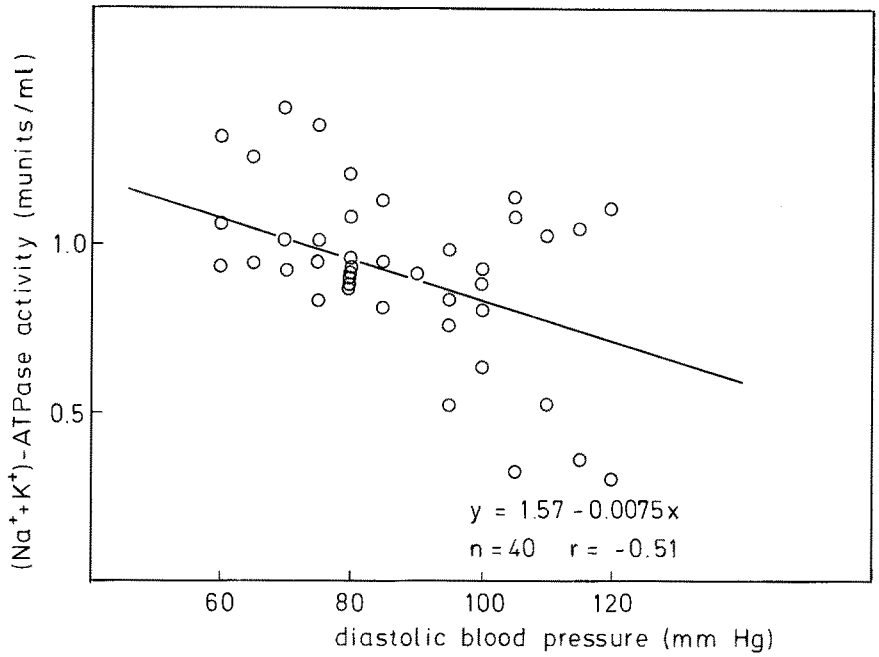

Fig. 2. Correlation between $(Na^+ + K^+)$-ATPase activity and diastolic blood pressure. 1.3 mU $(Na^+ + K^+)$-ATPase/ml were included in the test.

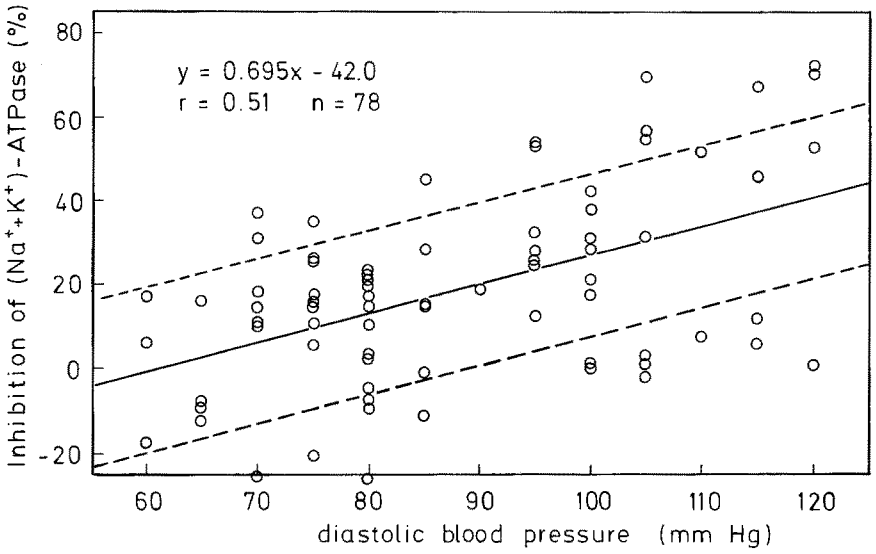

Fig. 3. $(Na^+ + K^+)$-ATPase inhibition as a function of the diastolic blood pressure using 1.3 mU/ml in the test system. The *dashed lines* indicate standard deviations of the regression line (*solid*).

negative correlation was found between the enzyme activity (y) and the diastolic blood pressure (x) (Fig. 2). A similar correlation coefficient ($r = -0.58$; $p < 0.001$) was obtained with the systolic blood pressure. When 78 sera were evaluated by calculating the percent inhibition of $(Na^+ + K^+)$-ATPase, their close correlation with the diastolic blood pressure was confirmed (Fig. 3).

By changing the amount of enzyme included in the assay, it was found that lowering the concentration of $(Na^+ + K^+)$-ATPase increased the relative degree of inhibition in the hypertensive sera (Table 2). At the enzyme concentration of 24.6 mU/ml, control assays without serum showed a marked difference not only in the hypertensives ($p < 0.005$) but also in the normotensives ($p < 0.05$).

Discussion

Ambrosioni et al. [2] have reported that the sodium content of lymphocytes from healthy donors increase when these cells are incubated in the serum of patients with essential hypertension. Therefore, lymphocytes seem to be a good tool for studying the influence of serum factors on the sodium pump. Our findings demonstrate that the active

sodium transport in lymphocytes from healthy donors is markedly decreased in the presence of serum from patients with essential hypertension, while the ouabain-insensitive transport remains unaffected. This confirms the findings of Poston et al. [28] who used leukocytes for their efflux studies. The existence of a serum factor acting on the sodium pump was reinforced by a corresponding effect of serum on the isolated $(Na^+ + K^+)$-ATPase. First, both assays revealed a close correlation between the concentration of the inhibitory substance(s) and the blood pressure of the serum donors. Second, the compound(s) were present in the serum of both hypertensives and normotensives. However, a causal relationship between the rise in blood pressure and the increased concentration of the inhibitor is still a subject of speculation.

Since the plot of $(Na^+ + K^+)$-ATPase inhibition shows a considerable scatter, which appears to increase with the degree of hypertension, this kind of assay cannot be used for diagnostic purposes. However, Morgan et al. [26] and Haddy and Pamnani [15], who studied $^{86}Rb^+$ uptake in rat-tail arteries, successfully demonstrated increased levels of an inhibitor of the sodium pump only in sera selected for low renin content. It remains to be tested whether such a selection is able to sort out sera of donors without elevated concentrations of a circulating inhibitor of $(Na^+ + K^+)$-ATPase but with essential hypertension.

At an enzyme concentration comparable to that reported by Hamlyn et al. [14], the $(Na^+ + K^+)$-ATPase inhibition in the hypertensive group also ranged below 10%. However, these authors applied the boiled and deproteinized supernatant, not the native serum that was used in our study. By including less $(Na^+ + K^+)$-ATPase in the assay, it was possible to make the test more sensitive and find conditions where a 45% inhibition of $(Na^+ + K^+)$-ATPase is detectable in the hypertensive group.

Our results demonstrate that the circulating inhibitor of the sodium pump acts on both sodium transport of intact cells and the isolated $(Na^+ + K^+)$-ATPase, which represents the specific receptor protein for cardiac glycosides. Assuming that the circulating inhibitor (I) acts like cardiac glycosides by forming an enzyme inhibitor complex (EI)

$$E + I \rightleftharpoons EI \qquad \text{Eq. (1)}$$

from the active enzyme (E), the law of mass action predicts that more inactive enzyme (EI) is formed when the amount of enzyme is increased. Furthermore, lowering the amount of $(Na^+ + K^+)$-ATPase in the test system should increase the relative inhibition of the enzyme. This effect was observed in our test system.

For these reasons it may be concluded that the inhibitory effects observed are due to a presumed endogenous digitalis. This assumption corresponds with the recent demonstrations of serum factors which cross-react with digoxin antibodies [6]. Since the concentration of the inhibitor cannot be quantified with the above assay, a quantitative assay must be developed. Work is in progress to see whether it is possible to determine the concentration of the circulating inhibitor by the competitive binding to the cardiac glycoside receptor site of $(Na^+ + K^+)$-ATPase.

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