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Intrinsic difference in erythrocyte membrane in spontaneously hypertensive rats characterized by Na^+ and K^+ fluxes

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Abstract. The goal of this study was to determine whether the elevated flux of sodium and potassium through the erythrocyte membrane of spontaneously hypertensive rats (SHR) is due to an intrinsic difference in the cell membrane or to a humoral factor present in the plasma. Isolated and washed erythrocytes from SHR and normotensive Wistar Kyoto (WKy) and Sprague-Dawley (SD) rats, were incubated in 1) a physiological salt solution, 2) WKy or SD plasma and 3) SHR plasma. Incubations were performed at 4°C for 23 h. Erythrocytes from SHR incubated in physiological salt solution had significantly greater Na^+ and K^+ fluxes than those from normotensive WKy and SD rats ($P < 0.005$). Plasma from any of the three strains of rats, as compared to physiological salt solution, increased Na^+ influx in the following order: SD > WKy > SHR. Erythrocyte K^+ efflux was not altered by plasma. We conclude that the elevated flux of Na^+ and K^+ in SHR erythrocytes is due to an intrinsic difference in the cell membrane. The greater Na^+ influx in plasma from any strain of rats is not correlated with the blood pressure of the rat. The lesser increase in Na^+ influx in erythrocytes incubated in plasma from SHR masks the greater intrinsic membrane permeability in the SHR erythrocyte when Na^+ fluxes are studied in whole blood. The elevated flux of Na^+ and K^+ through the erythrocyte membrane of SHR may reflect a general membrane defect that underlies the pathogenesis of elevated arterial pressure.

Key words: Hypertension – Sodium and potassium permeability – Plasma factor

Introduction

Abnormalities in fluxes of sodium and potassium have been demonstrated across erythrocyte membranes from spontaneously hypertensive rats (SHR) and humans with essential hypertension (see Table 1). These abnormalities include differences in Na^+/K^+-ATPase activity, Na^+/K^+-co-transport, Na^+/Li^+-countertransport and passive diffusion of monovalent cations. It has been suggested that a humoral factor is involved in transmembrane distribution of sodium and potassium in hypertension [26, 34, 36, 47]. In order to determine if a humoral factor is involved in the abnormal fluxes of Na^+ and K^+ across the erythrocyte membrane of SHR, plasma cross-over studies were performed, i.e., SHR erythrocytes incubated in plasma from normotensive Wistar Kyoto (WKy) or Sprague-Dawley (SD) rats and cells from normotensive rats incubated in SHR plasma.

Materials and methods

Blood pressures. Systolic blood pressures of 4–7 month old unanesthetized spontaneously hypertensive rats (SHR), and normotensive Wistar Kyoto (WKy) and Sprague-Dawley (SD) rats (Parke Davis or Taconic Farm) were monitored indirectly with a tail cuff and a Narco Pneumatic pulse transducer recorded on a Grass polygraph.

Blood. In each experiment one SHR and one normotensive control (SD or WKy) rat were used. Rats were anesthetized with 50 mg sodium pentobarbital per kg body weight ip. By cannulating the abdominal aorta, blood was drawn into a 10 ml syringe containing 100 units sodium heparin. Initial hematocrit values and whole blood hemoglobin concentrations were measured. One whole blood sample (2 ml) from each rat, i.e., erythrocytes suspended in their own plasma without any experimental manipulations, was incubated. The pH of these whole blood samples ranged from 7.38 to 7.42. Following overnight incubation at 4° C, the pH ranged from 7.61 to 7.65. The remaining 8 ml of blood were centrifuged, plasma and cells separated and buffy coat discarded. All centrifugations were performed for 10 min at 1,000 × *g*. Two 0.5 ml plasma samples were taken for initial Na^+ and K^+ concentration determination by flame photometry. Initial Na^+ and K^+ concentrations were also determined in two 0.5 ml samples of physiological salt solution (PSS).

Erythrocytes. Erythrocytes were washed twice at room temperature in PSS containing: NaCl (145 mM), KCl (4.5 mM), $MgSO_4 \cdot 7H_2O$ (1.22 mM), $Na_2HPO_4 \cdot 7H_2O$ (1.19 mM), $CaCl_2 \cdot 2H_2O$ (1.6 mM), dextrose (5.5 mM), fraction V bovine albumin (0.5%) and morpholino propane sulfonic acid (20 mM, MOPS). The pH was adjusted at 4° C to 7.4. After each wash, the cells were centrifuged and PSS was discarded. From each strain of rats, 1 ml of packed erythrocytes was resuspended in 1) 1 ml PSS (same as above), 2) 1 ml WKy or SD plasma and 3) 1 ml SHR plasma. In the experiments using plasma as a suspension medium, pH was not controlled.

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Table 1. Erythrocyte membrane characteristics in essential hypertension and in SHR

Species	Membrane characteristics	Abnormality[a] with references		
Human	permeability to Na^+	↑: [20, 24, 32, 33, 35, 47]		
SHR	permeability to Na^+	↑: [5, 10, 12, 14, 38, 48, 49]		
Human	Na^+/K^+ ATPase activity	↑: [20, 23, 45, 50]	↓: [24, 32, 34, 36]	
SHR	Na^+/K^+ ATPase activity	↑: [11, 12]		
Human	Plasma factor changing Na^+/K^+ ATPase activity		↓: [26, 34, 36, 47]	⟷: [45]
Human	Na^+/K^+ cotransport	↑: [1, 7]	↓: [7, 8, 21, 23, 25]	⟷: [13, 44]
SHR	Na^+/K^+ cotransport		↓: [11, 12]	
Human	Na^+/Li^+ countertransport	↑: [1, 6, 7, 8, 27]		
Human	Temperature dependence of Li^+-efflux			[31]
SHR	General review of erythrocyte membrane permeability as a genetic marker in SHR			[51]

[a] ↑ = increase; ↓ = decrease; ↔ = no difference

Incubation. All samples were incubated for 23 h at 4°C in 25 ml siliconized glass Erlenmeyer flasks connected to a wrist-action shaker. The shaker setting was selected so that the motion was minimal necessary to prevent erythrocyte sedimentation. Before and after incubation, hematocrit values were measured for each sample. After incubation, the samples were centrifuged and incubation media separated for final Na^+ and K^+ concentration determination. All measurements were performed in duplicate. Final incubation media hemoglobin concentrations were also measured.

Ionic flux. Ionic flux was measured extracellularly as a change in the ion concentration in the incubation media, (expressed as μEq/ml packed erythrocytes/23 h) and corrected for cell and plasma volume, by the following formula:

$$\text{Ionic flux} = \frac{\Delta[\text{ion}](1-H)}{H}$$

where Δ[ion] is the difference in concentrations of the ions in the medium before and after incubation, and "H" is the mean of hematocrit values taken before and after incubation. Hematocrits measured before and after incubations did not vary more than 1%. Microhematocrit centrifugations lasted for 2 min at 4,500 × g.

Hemolysis. In addition to albumin in the PSS, 20 μl of dextrose solution was added to each sample (final medium concentration 11.1 mM) to minimize hemolysis during the washing procedure and the incubation. The percentage of lysis was calculated by dividing the final concentration of hemoglobin in the medium by the whole blood hemoglobin concentration, both measured by the hemiglobincyanide method [30]. Hemolysis never exceeded 1.3%.

Statistics. The statistical significance was assessed by Student's "t" test. $P < 0.05$ were considered significant. Data are expressed as mean ± SEM.

Results

Blood pressures (Fig. 1), whole blood hematocrit values, whole blood hemoglobin concentrations and initial plasma

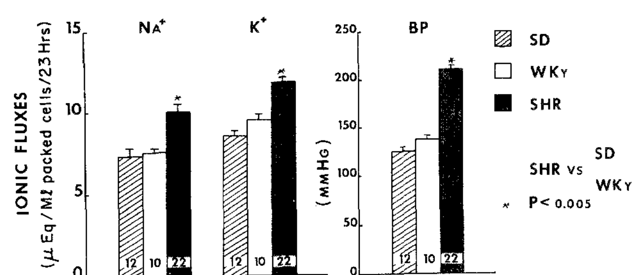

Fig. 1. Systolic blood pressures of SHR, WKy and Sprague-Dawley (SD) rats and ionic fluxes in their erythrocytes incubated in physiological salt solution (PSS). Numbers at bottom of columns denote number of animals studied

Table 2. Blood characteristics in three strains of rats

	Hematocrit %	Hemoglobin concentration (g/dl)	Initial plasma concentration (μEq/ml)		No. of animals
			Na^+	K^+	
SHR	50.9* (±0.4)	16.0* (±0.1)	140.1 (±0.4)	3.4 (±0.1)	22
WKy	47.1 (±0.7)	14.8 (±0.3)	139.6 (±0.3)	3.6 (±0.1)	10
SD	49.2 (±0.7)	15.6 (±0.4)	142.5 (±0.4)	3.4 (±0.1)	12

*$P < 0.01$; SHR vs WKy

Na^+ and K^+ concentrations are given in Table 2. Significant differences were observed between SHR blood pressures as compared to those from normotensive rats and between SHR whole blood hematocrits and hemoglobin concentrations when compared with those from WKy rats. SD initial plasma Na^+ concentrations were higher than those from SHR and WKy rats.

PSS incubation. SHR erythrocytes incubated in PSS showed a 30% greater Na^+ influx and a 30% greater K^+ efflux than

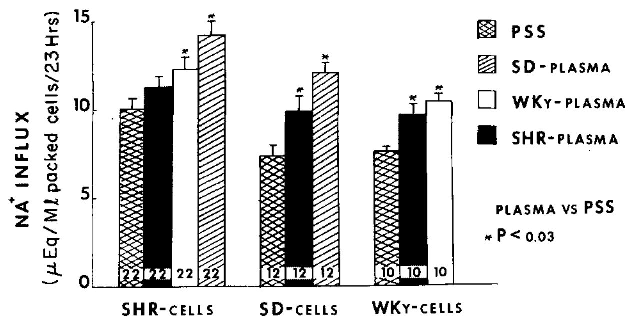

Fig. 2. Na^+ influx in erythrocytes from each strain incubated in PSS or in plasma from SHR, WKy and SD rats

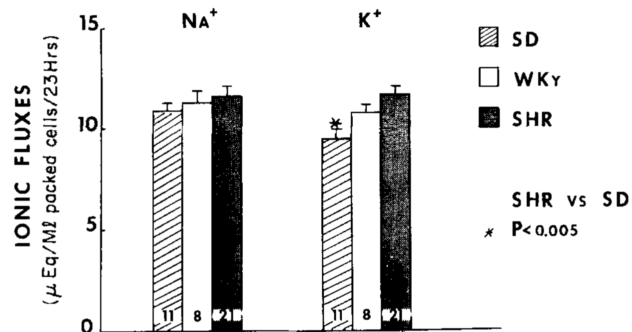

Fig. 4. Ionic fluxes in whole blood from SHR, WKy and SD rats

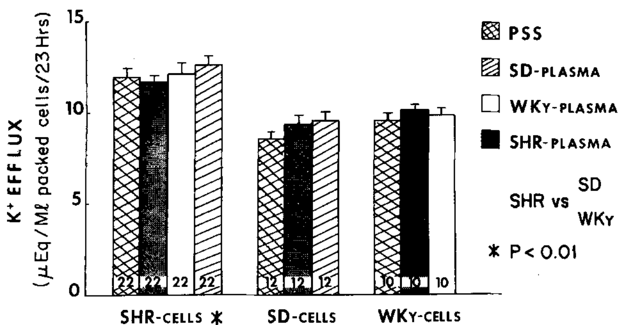

Fig. 3. K^+ efflux from erythrocytes from each strain incubated in PSS or in plasma from SHR, WKy and SD rats

similarly treated erythrocytes from either WKy or SD rats (Fig. 1).

Na^+ influx. Na^+ influx in SHR erythrocytes was higher than those in erythrocytes from normotensive rats when incubated in any one of the three plasmas or in PSS. Erythrocytes incubated in plasma showed greater Na^+ influx as compared to those incubated in PSS. In plasmas from the three strains of rats, Na^+ influx was increased in the following order: SD > WKy > SHR (Fig. 2).

K^+ efflux. Regardless of the incubation medium, K^+ efflux in erythrocytes from SHR was significantly higher ($P < 0.01$) than in erythrocytes from WKy and SD rats. Erythrocyte K^+ efflux was not altered by plasma (Fig. 3).

Whole blood incubations. No difference in Na^+ influx was observed among the three strains of rats. In SHR whole blood incubations, K^+ efflux tended to be higher than in those from WKy and SD rats (Fig. 4).

Discussion

Previous reports have indicated that there are abnormal fluxes of sodium and potassium across the membrane of the erythrocyte from SHR when compared to fluxes across this membrane from normotensive rats (Table 1). The purpose of this study was to determine whether this difference is due to: 1) an intrinsic difference in membrane properties or 2) an acute action of a humoral factor present in the plasma. We observed that erythrocytes from SHR had greater Na^+ and K^+ fluxes than those from normotensive WKy and SD rats when incubated in PSS or when incubated in the same plasma. Therefore, we conclude that the greater fluxes are due to an intrinsic difference between erythrocyte membranes of SHR and those of the normotensive strains of rats.

The current study does not give insight into the nature or cause of the difference. The studies were carried out at 4° C. At this temperature the active ion movement driven by Na/K-ATPase was considered to be negligible [41]. Furthermore, we observed that fluxes at 4° C did not change in the presence of 10^{-3}M ouabain (unpublished observations). Participation of the Na^+/K^+ cotransport at this temperature is also unlikely [43]. Sen et al. [42] observed that the erythrocytes of SHR were smaller than those of WKy. If this difference were of sufficient magnitude it would be responsible for a greater diffusion surface which could cause the greater flux of the SHR erythrocyte. However, calculated from the measurements of cell size by Sen et al. [42], the ratio of cell surface to cell volume in SHR was only 3.8% greater than this ratio in erythrocytes from WKy. Since the fluxes of Na^+ and K^+ were 25 to 30% greater in the erythrocytes of SHR than in those of WKy, it does not appear that the size of difference can account for the greater flux. Furthermore, as reasoned by Friedman et al. [16], "If this were due to a simple increase in the area available for diffusion, it would be equally evident at all temperatures" [11]. They observed that the difference was greater at 3° C than at higher temperatures. We have repeated comparative studies at 37° C (with and without ouabain) and at 4° C. No differences between fluxes of erythrocytes from SHR and WKy rats were observed at 37° C, whereas the expected difference was seen at 4° C (unpublished observation). This greater ion flux in the SHR erythrocyte than in that from WKy therefore probably reflects a greater passive cation leak of this membrane. The observations do not distinguish among the following possible causes of the abnormality in the erythrocyte membrane of the SHR: 1) an intrinsic genetic difference in membrane structure 2) a neurogenic or humoral influence on the membrane during erythropoiesis or 3) an action of a plasma factor that permanently alters this membrane. Furthermore, although plasma from SHR does not produce the characteristic change in erythrocyte fluxes at 4° C, the possibility remains that it might have an influence on the erythrocyte membrane if it were incubated at 37° C. Nevertheless, the basic observation that a flux difference does occur at 4° C in the absence of plasma establishes that this technique can be used to identify an intrinsic abnormality of the membrane of the erythrocyte in SHR. This difference is not dependent on the immediate presence of a component of plasma.

Erythrocytes incubated in plasma had consistently greater Na^+ fluxes than those incubated in PSS (Fig. 2). This effect does not parallel the elevation of blood pressure of hypertension; the increase in Na^+ influx in plasma from normotensive rats was greater than that in plasma from SHR. The lesser increase in plasma incubations from SHR compensates for the greater intrinsic permeability in the erythrocyte membrane from this strain, hence, when Na^+ fluxes are studied in whole blood, the more active intrinsic transport system of the erythrocyte membrane of the SHR is masked (Fig. 4). The mechanism of action by which Na^+ influx in plasma incubations is increased is not apparent from these studies. However since plasma contains bicarbonate (our PSS did not), and plasma incubations were not performed with CO_2 in the gas phase, it is possible that the increased Na^+ fluxes are due to alkalinization of the plasma [4, 17]. Furthermore, sodium can enter the cell as part of the anion $NaCO_3^-$. It is known that sodium but not potassium in this form can utilize the anion channel to traverse the erythrocyte membrane [18, 19].

Hematocrit and hemoglobin values were found consistently higher in the SHR (Table 2). These observations agree with those by Sen et al. [42].

The relation of altered erythrocyte cation transport to the pathogenesis of essential hypertension in humans or spontaneous hypertension in rats is unclear. Wessels et al. [47] and Garay et al. [22] have observed that the membrane alteration may be genetically linked to the hypertensive process. Na^+ flux in erythrocytes from normotensive subjects with a family history of hypertension was greater than that in erythrocytes from normotensive subjects without a familial history of hypertension [22, 47]. In the current study similar erythrocyte fluxes were observed in two unrelated strains of normotensive rats. One of these strains (WKy) was derived from the same parent strain as was the SHR. Nevertheless, the SHR differed phenotypically in both arterial pressure and erythrocyte fluxes from both of the normotensive strains. The genetic bases for hypertension and for the increased membrane fluxes appear together in the SHR strain. We do not have evidence to indicate whether this is a coincidental or fixed relationship between these two phenotypes.

Altered cation transport has been observed in adipocytes [39], leukocytes [3, 40], and intestinal smooth muscle from SHR [2]. An altered cation permeability in vascular smooth muscle from hypertensive animals [15, 28, 29], presumably underlies the increased reactivity and sensitivity of vascular smooth muscle [46], and this may be responsible for the increase in total peripheral resistance that causes the arterial pressure elevation. The intrinsic abnormality of the readily accessible erythrocyte membrane may serve as a marker for a more generalized cell membrane defect in hypertension.

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