Temperature Dependence and Bidirectional Cation Fluxes in Red Blood Cells from Spontaneously Hypertensive Rats

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SUMMARY The net passive influx of Na\(^+\) and efflux of K\(^+\) (orthodirection) through the red blood cell membranes from spontaneously hypertensive rats (SHR) were observed to be significantly higher (p < 0.05) than those of three strains of normotensive rats when the measurements were made at 4°C. Similar comparative studies, carried out at 37°C, in the absence or presence of ouabain, showed no difference in these fluxes through this membrane from SHR compared to those from Wistar-Kyoto (WKY) rats, one of the normotensive strains. A study was undertaken to determine the temperature at which the greater cation fluxes in SHR red blood cells occurred. The net fluxes of Na\(^+\) and K\(^+\) decreased as the temperature was reduced from 37° to 15°C, but a paradoxical increase in the fluxes was observed as the temperature was decreased from 15° to 4°C. Only with this temperature shift (15° to 4°C) was the increase in flux significantly greater in SHR than in WKY cells.

Subsequent studies were designed to determine whether the difference in the transport systems of red blood cells of SHR and WKY could be observed in fluxes of these cations in either direction across the membrane. For "reverse direction" flux studies, red blood cells were loaded with Na\(^+\) (to 130 mEq/liter cell water) and depleted of K\(^+\) (to 30 mEq/liter cell water) by incubation with the ionophore monensin. The reverse passive efflux of Na\(^+\) and influx of K\(^+\) at 4°C of cells from SHR were significantly greater than those of VVKY. Thus, the abnormality of the red blood cell membrane in SHR behaves as if it were just an increase in the size or number of pores through which Na\(^+\) and K\(^+\) diffuse freely at low temperatures. (Hypertension 6: 42–48, 1984)

KEY WORDS • hypertension • membrane • Na\(^+\), K\(^+\) fluxes • monensin

ALTERED ion transport in red blood cells from SHR and patients with essential hypertension have been reported by many laboratories. These abnormalities include an increased activity of the Na\(^+\)-, K\(^+\)-ATPase,\(^1\)\(^-\)\(^2\) a decreased activity of the Na\(^+\)-K\(^+\) cotransport system,\(^3\)\(^-\)\(^4\) an increased activity of the Na\(^+\)-Li\(^+\) countertransport system,\(^5\)\(^-\)\(^6\) an increased Na\(^+\)/Na\(^+\) exchange,\(^7\) and an increase in the passive diffusion of Na\(^+\) and K\(^+\) across the red blood cell membrane.\(^7\)\(^-\)\(^8\) Increased Na\(^+\)-Li\(^+\) countertransport has also been reported in red blood cells from the normotensive sons of hypertensive parents.\(^9\)

A temperature-dependent alteration in the fluxes of Na\(^+\) and K\(^+\) through the red blood cell from SHR has been reported by Friedman et al.\(^7\) They noted that these ions move more freely downhill along their transmembrane concentration gradients in cells from SHR than they do in those from two normotensive control strains. The current study was designed to characterize these observations over a wider temperature range and to determine whether this membrane abnormality could be detected by fluxes of Na\(^+\) and K\(^+\) in either direction across the red blood cell membrane.

Methods

Male rats obtained from Taconic Farms were given food (Purina Laboratory Rat Chow) and water ad libitum. At the time of bleeding they weighed between 250 and 300 g.

Blood Pressure Measurement

Blood pressures from restrained, unanesthetized rats were measured indirectly by the tail cuff method. The output of the Narco pneumatic pulse transducer was recorded on a Grass polygraph. Triplicate readings were taken and averaged for each rat.

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Blood Sampling
Rats were anesthetized with sodium pentobarbital (50 mg/kg body wt) i.p. The abdominal aorta was cannulated and 9–12 ml of blood were drawn into a syringe containing 150 units of heparin. The blood was centrifuged for 6 minutes at 1700 g, and the plasma and buffy coat were removed by aspiration. Packed red blood cells were washed three times at room temperature in physiological salt solution (PSS) containing (mM): NaCl, 140; KCl, 5; MgSO₄ • 7H₂O, 1.22; Na₂HPO₄ • 7H₂O, 1.19; CaCl₂ • 2H₂O, 1.6; dextrose, 11.1; fraction V bovine albumin (0.25%); morpholino propane sulphonic acid (MOPS), 2.0; (pH = 7.4 at 25°C). Albumin and dextrose were added to the PSS to minimize hemolysis during the washing and incubation. After each wash the cells were centrifuged 6 minutes at 1700 g and the PSS discarded.

Incubation
After three washes, 1.5 ml of packed red blood cells were resuspended in an equal volume of PSS in a 25 ml siliconized glass Erlenmeyer flasks and incubated with gentle shaking to prevent sedimentation. Before incubation, hematocrit and hemoglobin values of the cell suspension were measured. A 1-ml aliquot was removed and centrifuged for determination of intracellular and extracellular concentrations of Na⁺ and K⁺. After incubation, hematocrit values were again measured and the samples were centrifuged. Measurement of final Na⁺ and K⁺ concentrations were made on the incubated PSS and on the packed cells. Final hemoglobin concentrations of the PSS were also determined.

Temperature Dependence
Incubations at 4°C were carried out in stoppered Erlenmeyer flasks which were mounted in a Burrell Wrist-Action Shaker (Burrell Corporation, Pittsburgh, Pennsylvania) in a walk-in refrigerator. Incubations at 37°C and 26°C were performed in a thermoregulated Lab-Line Shaker Bath. For studies below room temperatures, the Lab-Line Shaker Bath was placed in the walk-in refrigerator and adjusted to the desired temperature. The experiment at 0°C was also carried out in the walk-in refrigerator, with crushed ice continuously present in the Lab-Line Shaker Bath.

Determination of Ionic Fluxes
Ionic flux was measured as a change in the ion concentration in the PSS, and adjusted for red blood cell volume shifts as measured by hematocrit changes. The following formula was used to quantify this flux, which was expressed as mEq/liter packed cells/unit time:

\[
\text{Ionic flux} = \frac{[\text{ion}]_{A}(t-H_{A}) - [\text{ion}]_{B}(t-H_{B})}{H_{A}}
\]

where: [ion]ₐ = ion concentration in PSS after incubation; [ion]ₐ = ion concentration in PSS before incubation; Hₐ = value of hematocrit after incubation (X 0.99); and Hₐ = value of hematocrit before incubation (X 0.99).

Hematocrits were determined using Clay-Adams microhematocrit tubes centrifuged at 4500 g for 2 minutes. Na⁺ and K⁺ concentrations were determined on an Instrumentation Laboratory Flame Photometer (Instrumentation Laboratory, Inc., Lexington, Massachusetts). Hemoglobin concentration was determined by the cyanmethemoglobin method of Van Kampen and Zijlstra.¹⁰ The percentage of lysis was determined by dividing the hemoglobin concentration in the PSS after incubation by the hemoglobin concentration of the erythrocyte suspension in the PSS before incubation. Hemolysis rarely exceeded 1.0% and never exceeded 1.5%.

Na⁺ Loading and K⁺ Depletion
Monensin, a carboxylic ionophore, was used to load the red blood cell with Na⁺ and deplete the cell of K⁺. PSS was made hyperosmotic (H-PSS) by adding sucrose to the normal PSS. The osmolarity of the H-PSS was 350–370 mOsm compared to 290 mOsm of normal PSS. This H-PSS greatly decreased the hemolysis and cell swelling otherwise produced by treating the cells with monensin, 3 × 10⁻⁶ M.

Packed red blood cells from each rat were incubated for 30 minutes in 15 volumes of H-PSS containing monensin. Duplicate hematocrit determinations were made of the content of each flask before and after incubation. Following this loading period, cell suspensions were centrifuged 6 minutes at 1700 g and the PSS was saved for Na⁺ and K⁺ determinations. The cells were then washed four times in a washing PSS (W-PSS) of the following composition (mM): NaCl, 60; KCl, 60; sucrose, 48; MOPS, 2; albumin, 0.5%; (pH = 7.4 at 25°C). The extra albumin was added to this solution to increase the displacement of monensin from the red blood cell membrane (Pressman, personal communication). Two additional washes were carried out with a low sodium-PSS (L-PSS) containing (mM): KCl, 112; MgSO₄ • 7H₂O, 1.22; Na₂HPO₄ • 7H₂O, 1.19; MOPS 2.0; CaCl₂ • 2H₂O, 1.6; dextrose, 11.1; sucrose, 60; albumin 0.25% (pH = 7.4 at 25°C). Intracellular concentrations of Na⁺ and K⁺ were measured after the six washes and before reverse flux experiments.

Determination of Intracellular Na⁺ and K⁺
Cells were washed twice with 10 volumes of ice-cold isotonic MgCl₂ (110 mM) and Tris HCl (10 mM, pH 7.4 at 25°C). After each wash, samples were centrifuged for 6 minutes at 1700 g. After the second wash, 0.5 ml of packed cells was resuspended in 1 ml of this isotonic MgCl₂ solution. After mixing, duplicate hematocrit determinations were made of this suspension. Then 0.5 ml of this suspension was added to 4.5 ml of 16.7 mM LiNO₃, hypotonic lysing solution, to make a 1 in 10 dilution. Further dilution of 0.5 ml of this hemolysate was done with 4.5 ml of 15.0 mM LiNO₃ solution to make a 1 in 100 dilution. The concentrations of Na⁺ in the first dilution and of K⁺ in the second dilution were determined by flame photometry. Cell Na⁺ and K⁺, expressed as mEq/liter packed cells
were then calculated by dividing the ionic concentrations by the hematocrit and multiplying by the dilution correction factor.

**Determination of Cell Water**

Packed red blood cells (0.5 ml), the hematocrit (Hct) of which had been determined, were pipetted into a tared glass test tube. The tube was weighed before and after drying at 80°C to a constant weight (24 hours), and determinations carried out as follows:

\[
\text{% water in RBC} = \frac{\text{wet weight} - \text{dry weight}}{\text{wet weight}} \times 100 - \left(100 - \text{Hct}\right) \times \frac{100}{\text{Hct}}.
\]

**Statistics**

Statistical evaluation of the data was by the Student's t test for paired samples. Samples studied on the same day were considered to be paired. The 0.05 level of probability was regarded as significant.

**Results**

**Temperature Dependence of Na\(^+\) and K\(^+\) Fluxes**

The net flux of sodium and potassium through the red blood cell membrane from SHR were significantly higher than those through these membranes from each of three strains of normotensive rats (WKY, Sprague-Dawley, Long Evans) when compared at 4°C (Table 1). These are primarily passive fluxes in which Na\(^+\) and K\(^+\) move down their physiologically occurring concentration gradients (designated "orthodirectional fluxes").

The results of similar studies, carried out at 37°C in the presence or absence of 3.0 mM ouabain, are presented in Figure 1. There was no difference in fluxes between red blood cells from SHR and WKY in the absence of ouabain. Likewise, there was no difference between the cells from these two strains of rats when the ouabain-sensitive or the ouabain-insensitive components of these fluxes were compared at 37°C.

Because of this difference in results between studies carried out at 4° and 37°C, observations were next made at temperatures between 4°C and 37°C, all in the presence of ouabain. The flux of Na\(^+\) and K\(^+\) decreased in magnitude as the temperature decreased from 37° to 15°C, but a paradoxical increase in the flux of Na\(^+\) and K\(^+\) occurred as the temperature was decreased from 15° to 4°C (Figure 2). Table 2 demonstrates that, whereas there was no difference between red blood cell fluxes of SHR and WKY at 15°C, the difference was significant at 4°C. No difference between red blood cells from SHR and WKY was seen in their degrees of lysis or hematocrit changes at these temperatures. A further study showed that there were no different K\(^+\) fluxes through the red blood cell membranes from SHR and WKY rats at 15° and 11°C; however, as the temperature was lowered to 7°, 4°, or 0°C, the differences between K\(^+\) fluxes through the red blood cell membranes from SHR and those from WKY were progressively greater (Figure 3). Differences in Na\(^+\) fluxes between red blood cells from SHR and WKY were similarly temperature dependent.

**Red Blood Cell Loading of Na\(^+\) and Depletion of K\(^+\) by Monensin**

The action of monensin as an ionophore permits the rapid dissipation of transmembrane gradients of Na\(^+\) and K\(^+\). It can be used to load the red blood cell with Na\(^+\) and to deplete the cell of K\(^+\). It acts in a concentration-dependent fashion and the ions reach equilibrium rapidly (15-30 minutes). At a concentration of 10⁻⁵ M, monensin causes cell swelling and hemolysis; however, using a hyperosmotic PSS and monensin at a

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**Table 1. Ionic Fluxes at 4°C of Red Blood Cells and Blood Pressures in Four Strains of Rats**

<table>
<thead>
<tr>
<th></th>
<th>SHR</th>
<th>LE</th>
<th>SD</th>
<th>WKY</th>
</tr>
</thead>
<tbody>
<tr>
<td>Na(^+) influx</td>
<td>0.34 ± 0.03(6)</td>
<td>0.25 ± 0.02(6)*</td>
<td>0.21 ± 0.02(6)*</td>
<td>0.25 ± 0.04(5)*</td>
</tr>
<tr>
<td>K(^+) efflux</td>
<td>0.41 ± 0.03(6)</td>
<td>0.27 ± 0.01(6)*</td>
<td>0.25 ± 0.01(6)*</td>
<td>0.29 ± 0.04(5)*</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>200 ± 3(6)</td>
<td>123 ± 3(6)*</td>
<td>130 ± 3(6)*</td>
<td>130 ± 5(5)*</td>
</tr>
</tbody>
</table>

Fluxes expressed in mEq ion/liter packed cells/hr, ± SEM. Flucts were carried out for 23 hours. SHR = spontaneously hypertensive rats; LE = Long Evans; SD = Sprague-Dawley; and WKY = Wistar-Kyoto normotensive rats. Parentheses indicate number of rats. Asterisks indicate significant difference from SHR where p < 0.05.

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**Table 2. Passive Fluxes of Na\(^+\) and K\(^+\) in Red Blood Cells from SHR and WKY at 4° and 159°C in the Presence of 3 mM Ouabain**

<table>
<thead>
<tr>
<th>Rat group</th>
<th>4°C</th>
<th>15°C</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na(^+)</td>
<td>K(^+)</td>
</tr>
<tr>
<td>WKY</td>
<td>0.32 ± 0.04(10)</td>
<td>0.45 ± 0.02(10)</td>
</tr>
<tr>
<td>SHR</td>
<td>0.42 ± 0.03(10)*</td>
<td>0.60 ± 0.03(10)*</td>
</tr>
</tbody>
</table>

Data expressed as mEq ion/liter packed cells/hr, ± SEM. Parentheses indicate number of rats. *p < 0.05 as compared to WKY. †p < 0.005 as compared to WKY.
Figure 1. Sodium and potassium fluxes across the red blood cell membrane at 37°C in the presence and absence of 3 mM ouabain. Negative fluxes indicate movement of ions against their concentration gradients. The ouabain-sensitive component (active transport) was calculated as the difference between the fluxes in the presence and absence of ouabain. The ratio of Na⁺/K⁺ ouabain-sensitive fluxes was 1.54 for WKY and 1.44 for SHR. There were no differences between SHR and WKY in any type of Na⁺ or K⁺ flux. Brackets represent SEM.

Figure 2. Potassium efflux through the red blood cell membrane down its concentration gradient, in the presence of 3 mM ouabain. The fluxes were determined at four different temperatures: 37°C, 26°C, 15°C, and 4°C. Data are the means of triplicate determinations of red blood cell fluxes of a single pair of SHR and WKY.

Figure 3. Potassium efflux through the red blood cell membrane from SHR and WKY rats at five different temperatures. All experiments were done in the presence of 3 mM ouabain. The K⁺ effluxes were significantly greater through the red blood cell membranes from SHR than through those from WKY at 7°C, 4°C, and 0°C. No differences were observed at 11°C and 15°C. Data are the means of determinations of red blood cell fluxes in six pairs of rats. Brackets represent SEM.
concentration of $3 \times 10^{-6} \text{M}$, the cells could be effectively loaded in 30 minutes at 37°C with little hemolysis (less than 0.1%).

A study was performed to determine whether this use of monensin had any residual effect on the passive membrane properties of the red blood cell after a thorough washout procedure (Figure 4). Cells were incubated with monensin ($3 \times 10^{-6} \text{M}$) for 30 minutes at 37°C in a PSS that contained the normal intracellular concentrations of Na$^+$ and K$^+$. These cells were monensin-treated but their intracellular Na$^+$ and K$^+$ concentrations were not changed. After washing out the monensin (six washes), passive fluxes of Na$^+$ and K$^+$ down their concentration gradients of these cells were compared with cation fluxes of appropriate control cells. Figure 4 shows that there was no residual ionophore action in the monensin-treated cells. These results suggest that monensin is thoroughly washed out of the cells. We have also observed that the difference in the orthodirectional fluxes at 4°C between SHR and WKY still occurs in these monensin-treated cells after the monensin has been washed out.

Reverse Direction Fluxes

The intracellular concentrations of sodium and potassium (expressed as mEq/liter cell water), after incubating the red blood cells at 37°C for 30 minutes in hyperosmotic PSS containing $3 \times 10^{-6} \text{M}$ monensin, were not different for red blood cells from SHR and WKY (Table 3). The low sodium, high potassium PSS, in which the sodium-loaded cells were incubated for 23 hours at 4°C and hence the fluxes were again passive with no increase in cell water after the monensin treatment as demonstrated by the absence of change either in hematocrit or in wet and dry weight ratio of the red cells, before and after incubation.

Studies of fluxes in the reverse direction, i.e., Na$^+$ efflux and K$^+$ influx, were also carried out for 23 hours at 4°C and hence the fluxes were again passive with Na$^+$ and K$^+$ moving down their concentration gradients. Under these conditions, when net transmembrane movements of Na$^+$ and K$^+$ were normalized for their respective concentration differences, it was evident that fluxes were significantly greater in the reverse direction than in the orthodirection (Figure 5). In this reverse direction, the net Na$^+$ and K$^+$ fluxes through the red blood cell membrane were also greater for SHR when compared to those for WKY.

![Figure 4. Electrolyte fluxes after washout of monensin.](image)

**Figure 4.** Electrolyte fluxes after washout of monensin. Mean ± SEM of net Na$^+$ influx and K$^+$ efflux through red blood cell membranes incubated for 23 hours at 4°C. Control red cells were not manipulated. "Washed Only" cells were washed six times with low Na$^+$ PSS. "Monensin Incubated and Washed" cells were incubated in $3 \times 10^{-6} \text{M}$ monensin in a low Na$^+$ PSS and washed six times, and "PSS Incubated and Washed" cells were incubated 30 minutes at 37°C in a low Na$^+$ PSS and then washed six times. There were no significant differences between any of the electrolyte fluxes.

![Figure 5. Ortho- and reverse direction fluxes normalized to concentration differences of 100 mEq across the cell membrane.](image)

**Figure 5.** Ortho- and reverse direction fluxes normalized to concentration differences of 100 mEq across the cell membrane. Reverse direction electrolyte fluxes were from cells that were Na$^+$ loaded and K$^+$ depleted. Cells used for reverse direction flux studies were incubated in a low Na$^+$ (5 mM), high K$^+$ (110 mM) PSS for 23 hours at 4°C. Na$^+$ and K$^+$ fluxes were greater through red blood membranes from SHR when compared to those from WKY in either direction. Asterisk indicates a level of flux difference from the WKY cells in which $p < 0.05$. Brackets represent SEM.

### Table 3. Intracellular Na$^+$ and K$^+$ after Monensin Loading

<table>
<thead>
<tr>
<th>Rat group</th>
<th>Red blood cells</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Na$^+$</td>
</tr>
<tr>
<td>WKY</td>
<td>88.7 ± 0.2(7)</td>
</tr>
<tr>
<td>SHR</td>
<td>87.6 ± 0.5(7)</td>
</tr>
</tbody>
</table>

Data expressed in mEq ion/liter packed cells ± SEM. Parentheses indicate numbers of rats.
Discussion

The greater Na\(^+\) and K\(^+\) fluxes of the red blood cells of SHR compared to those of the WKY could reflect either a greater diffusion area or an intrinsic increase in leakage of the cell membrane. Sen et al.\(^1\) observed that the red blood cells of SHR were smaller than those of WKY. If this difference in size were sufficiently great, the increase in surface area of the smaller SHR cells could be responsible for the greater fluxes. However, if this were the cause of the difference, the greater fluxes should occur at all temperatures. Since this is not the case, it must be concluded that there is an intrinsic difference between the red blood cell membranes of these two strains of rats, and that the effects of this difference are more prominent at reduced temperature.

Results of the current studies confirm the earlier work of Friedman et al.\(^7\) demonstrating that there is a difference between the red blood cell membranes of SHR and those of normotensive rats and that this difference is unmasked at temperatures below 10°C. At these temperatures, the membrane characteristic of both types of cells changes, so that the fluxes of Na\(^+\) and K\(^+\) are greater. This change is significantly larger in the membrane from the SHR. Although the greater passive fluxes of Na\(^+\) and K\(^+\) in the red blood cell at low temperatures have been known for over 12 years,\(^12\) the molecular basis for the increase is still not understood. Our findings indicate that it is this molecular mechanism that differs quantitatively between the red blood cells of the SHR and those of the WKY.

Levy et al.\(^13\) have recently made another observation indicating that there is a temperature-dependent abnormality in red blood cell membrane in hypertension. They studied Li efflux from red blood cells and reported a modified temperature dependence of this flux in cells from patients with essential hypertension. They observed that the rate of ouabain-resistant Li efflux in normotensive subjects had a pattern of temperature dependence with two slopes that had an inflection point at about 25°C. Red blood cells from patients with essential hypertension, however, showed a higher Li efflux and a significant difference in the temperature dependence, with essentially a single slope. They concluded that their data indicated localized changes in membrane organization in the red blood cell from patients with hypertension, possibly involving lipid-protein interaction. Thus, it appears that both the SHR and the patient with essential hypertension have a red blood cell membrane abnormality that is temperature dependent.

To determine whether the transport system responsible for the higher flux of Na\(^+\) and K\(^+\) in SHR membrane was bilaterally symmetrical, reverse fluxes of these cations were studied. Cell sodium was increased and cell potassium decreased by incubating the cell suspension in the presence of monensin, a carboxylic ionophore. This ionophore was effective in letting sodium in and potassium out of the cell. Monensin could readily be washed out of the membrane. Brock and Smith\(^14\) have shown that this ionophore is also readily washed out of the vascular smooth muscle membrane.

Our results show that, after exposure to monensin and a thorough washout, normal passive membrane fluxes return. Nevertheless, reverse-direction fluxes were greater than ortho-directional fluxes in red cells from both strains of rats. High concentrations of Na\(^+\) inside the cell and K\(^+\) outside are known to stimulate Na\(^+\)-K\(^+\) pump.\(^15\) Even at low temperatures (0–10°C), the pump has been shown to be slightly active (0.2% to 0.8% of activity measured at 37°C).\(^16\) Furthermore, our observations indicate that orthodirectional fluxes in the presence of ouabain are slightly greater than those in its absence (compare Tables 1 and 2). The high intracellular sodium and extracellular potassium may stimulate the pump and this would facilitate movement of these ions in the "reverse" direction. Under these conditions, the reverse directional Na\(^+\) efflux and K\(^+\) influx were still greater for red blood cells of SHR as compared to those of WKY.

Altered membrane transport in patients with essential hypertension and in rats with genetic hypertension may be an underlying fault that leads to the development of elevated arterial blood pressure.\(^17\)–\(^18\) Exaggerated fluxes of K\(^+\) and Na\(^+\) similar to those in the red blood cells have been observed in vascular smooth muscle from SHR and from rats with other types of experimental hypertension.\(^19\)–\(^23\) This increased leakiness of the vascular smooth muscle cell may well be the cause of the increase in smooth muscle sensitivity and hence increase in vascular resistance that causes hypertension.\(^24\) The observation of a similar membrane abnormality in the red blood cell, although here it is unmasked only at a low temperature, suggests that this cell may be used as a marker in hypertension. Also, because of its availability and relative ease of study, it can be used to characterize a membrane fault in hypertension.

Our results demonstrate that the abnormality of the membrane of the red blood cell of SHR could be detected as a greater flux of Na\(^+\) and K\(^+\) in either direction. The channels through which these increases in fluxes occur at temperatures below 10°C appear to be bilaterally symmetrical and do not distinguish between Na\(^+\) and K\(^+\). These observations are compatible with the possibility that there is, at low temperatures, simply a greater number or size of the channels through which Na\(^+\) and K\(^+\) diffuse down their concentration gradients.

References


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