Abnormal whole-body and cellular (erythrocytes) turnover of $^{22}\text{Na}^+$ in normotensive relatives of probands with established essential hypertension

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Summary

1. Whole-body elimination rate of $^{22}\text{Na}^+$ was decreased in normotensive or borderline first-degree relatives of hypertensive probands.
2. Whole-body potassium; exchangeable sodium and urine excretion of sodium, potassium and creatinine were similar in relatives and controls.
3. Erythrocyte net influx of $^{22}\text{Na}^+$ was significantly increased in normotensive relatives.
4. Abnormal whole-body and cellular handling of sodium ($^{22}\text{Na}^+$) demonstrated in relatives indicates that this abnormality may have an important role in the development of essential hypertension in man.

Key words: erythrocyte net influx, normotensive relatives, sodium metabolism.

Introduction

Several studies from different populations (Prior, Evans, Harvey, Davidson & Lindsey, 1968; Dahl, 1972; Dawber, Kannel, Kagan, Donabedian, McNamara & Pearson, 1967) indicate a positive relationship between sodium chloride intake and prevalence of essential hypertension, but studies within single populations have given discrepant results. Rat experiments have indicated a genetic susceptibility to normal or high intakes of sodium chloride in some spontaneously hypertensive strains (Dahl, Heine & Tassinari, 1962). Various mechanism have been proposed (Postnov, Orlov, Gulak & Shevchenko, 1976; Friedman, Nakashima & McIndoe, 1977; Ganguli, Tobian & Iwai, 1979). It has been proposed that there is a genetic susceptibility to NaCl in man that predisposes to hypertension (Fries, 1976).

Dahl, Lax, Young, Schackow & Knudsen (1966) failed to confirm his early findings of an abnormal whole-body turnover of $^{22}\text{Na}^+$ in patients with established essential hypertension, but the genetic background was not studied. There is an increased net influx of $^{22-24}\text{Na}^+$ in erythrocytes of hypertensive patients (Wessels, Junge-Hälling & Losse, 1967) together with increased leucocyte intracellular sodium content and a decreased sodium efflux (Edmondson, Thomas, Hilton, Patrick & Jones, 1975).

In this work we have investigated the whole-body turnover of $^{22}\text{Na}^+$ in first-degree relatives of hypertensive probands as well as the net influx of $^{22}\text{Na}^+$ in erythrocytes.

Material and methods

Subjects

All first-degree relatives in the present study belonged to families with a history of established essential hypertension for at least two generations. Controls were normotensive, age-, sex- and weight-matched individuals without hypertension in their families during two generations.

In study A whole-body turnover of $^{22}\text{Na}^+$ was investigated in 24 first-degree relatives (four females, 20 males) and 15 controls (two females,
13 males). In study B erythrocyte net influx of $^{22}\text{Na}^+$ was studied in 35 first-degree relatives (15 females, 20 males) and 24 controls (10 females, 14 males).

Both methods have been applied on 11 first-degree relatives and 10 controls.

Study A

Whole-body potassium ($^{40}\text{K}$ activity) was measured in the low-background iron room. After background scanning with two opposite NaI(Tl)-detectors the individuals were injected with 20–50 kBq of $^{22}\text{Na}^+$ intravenously. Total exchangeable sodium was calculated after 24 h. The subjects maintained their usual diet and were scanned five times for the elimination rate over 8 days (days 0–8). Five urine collections (24 h) were obtained, and also plasma samples for measurements of $^{23}\text{Na}^*$ and $^{23}\text{Na}^+$ were taken. Twelve first-degree relatives and 11 controls continued the study (days 8–15) by adding NaCl (12 g daily) to their dietary sodium intake.

Study B

Blood was drawn into heparinized vessels and studied within 45 min. The packed erythrocytes were washed once with 1 vol. of the incubation solution (Dulbecco & Vogt, 1954) also containing glucose (8.84 mmol/l) human albumin (5.0 g/l) and $^{22}\text{Na}^+$ (37 MBq/l). A portion (2 ml) of the packed erythrocytes was incubated at 37°C with 2 ml of incubation solution. Aliquots were taken after 80 and 140 min and applied on a Sephadex G 50 (fine) column (20 cm long, 1.6 cm diameter; rate 1 ml/min) (Kantura, Kurashina & Nakao, 1974). Tris buffer, 0.15 mol/l with NaCl (153 mmol/l), pH 7.4, was used as effluent. Three erythrocyte fractions from the void were counted for $^{22}\text{Na}^+$ radioactivity in a Nukab Scintillator (350–1550 keV) after measurement of packed cell volume. Intra-assay and intra-individual accuracy was 1–3% (SD).

In study A blood pressure and heart rate were measured by nurses at 13.00–15.00 hours. In study B pressure was measured at 08.00–09.00 hours with an automatic pressure-recording apparatus (Bosomat, Boehringer Ingelheim) each minute for 10 min. Urine collections (24 h) were measured for sodium, potassium and creatinine.

Results

Study A

Whole-body elimination rate (%/day) and the biological half-life ($t_{0.5}$ days) of $^{22}\text{Na}^+$ were significantly ($P < 0.01$) different in first-degree relatives (5.8%/day; $t_{0.5} = 12.7 \pm 3.1$ days) compared with controls (7.3%/day; 9.8 \pm 1.5 days) during period 1 (Fig. 1). During days 8–15

![Fig. 1. Study A: $^{22}\text{Na}^+$ half-life as a function of 24 h urinary sodium excretion: •, first-degree relatives, and ○, controls, on normal diet; ▲, relatives, and △, controls, on normal diet plus 12 g of NaCl/day in tablet form. Mean values for each period are used for daily urinary Na$^+$ excretion.](image-url)
the elimination rate was equal in the two groups (first-degree relatives: 11-0%/day; controls: 11-4%/day).

The mean sodium output (24 h) during period 1 was equal (first-degree relatives: 147 ± 37 mmol; controls: 154 ± 14 mmol).

Whole-body potassium (first-degree relatives: 48.3 ± 7.3; controls: 49.8 ± 6.3 mmol/kg) and total exchangeable sodium (first-degree relatives: 37.3 ± 4.9; controls: 38.6 ± 4.1 mmol/kg), plasma and urine elimination rate of 22Na+, mean age (first-degree relatives: 33 ± 5 years; controls: 32 ± 5) and extrarenal excretion of 22Na+ during period 1 (11 first-degree relatives: 17.2%, 10 controls: 14.8%) were all equal in the two groups.

Blood pressure was significantly higher (P < 0.01) in first-degree relatives (140 ± 14/88 ± 9 mmHg) than in controls (124 ± 10/77 ± 8 mmHg). Heart rate was equal. Seventeen first-degree relatives were normotensive (<135/90 mmHg) and seven were borderline (<150/100 mmHg).

**Study B**

After 140 min of incubation the net influx of 22Na+ in erythrocytes was significantly increased in both males (P < 0.01) and females (P < 0.05).

Δ(Net influx) was only significantly increased (P < 0.01) in male first-degree relatives (244 ± 46 Bq/ml of erythrocytes) against male controls (191 ± 56 Bq/ml). Net influxes at both 80 and 140 min were significantly (P < 0.01) increased in both male groups compared with corresponding female groups.

Diastolic blood pressure was positively but not significantly correlated (r = 0.37, P < 0.1) to Δ(Net influx) in males.

The mean age was equal in the two groups (31 ± 4 years).

Blood pressures in males (relatives: 124 ± 10/80 ± 8; controls: 121 ± 10/75 ± 10) were equal, but the diastolic pressure in female relatives was significantly higher (P < 0.05) than in controls (relatives: 111 ± 8/78 ± 6; controls: 108 ± 8/71 ± 10). Heart rate was significantly higher (P < 0.05) in female first-degree relatives. Urine volume, sodium, potassium and creatinine excretion were equal in the two groups.

In the 11 first-degree relatives and 10 controls in whom both investigations had been carried out, the whole-body elimination rate was significantly decreased (P < 0.05) and the net influx of 22Na+ significantly increased (P < 0.05) in first-degree relatives.

In both studies there were no significant differences in weight, height and skinfold thickness.

**Discussion**

The biological half-life of 22Na+ in controls (9.8 ± 1.5 days) is exactly the same as that found by Dahl et al. (1966) under metabolic ward conditions. The exchangeable sodium, whole-body potassium and NaCl intake were also closely similar. Increased intracellular content of sodium or an abnormally slow intracellular exchange of a fraction of the sodium compartment (Garay, Moura, Osborne-Pellegrin, Papadimitriou & Worcel, 1979) could explain the reported findings.

An increase in intracellular sodium, which is only 20–25% of the total exchangeable sodium, would be very difficult to determine with the presently available methods for exchangeable sodium measurement. The increased net influx of 22Na+ in erythrocytes might indicate an abnormally slow intracellular exchange of sodium, which may be explained by an increased sodium content or a slow exchange in a fraction of it. There seem to be a marked difference in cell handling of sodium between the sexes; this has not been reported before. The significantly increased 22Na+ net influx in first-degree relatives indicates that it may play an important role in the development of essential hypertension in man.

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**References**


