Seventh Symposium on Salt, Vol. II 279–286 (1993)
Elsevier Science Publishers B.V., Amsterdam

Sodium Kinetics in Salt-Sensitive and Salt-Resistant Normotensive and Hypertensive Man

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ABSTRACT

We tested the hypothesis that sodium (Na) kinetics are not affected by blood pressure, salt-sensitivity, salt-resistance, or race (white Americans compared to African-Americans), as well as the hypothesis that the kinetics of Na balance are not a first order process. Two protocols were conducted. In the first, 18 normal and 36 hypertensive men and women were given 120 mmol/d Na for 6 days, followed by 10 mmol/d for 8 days, and by 400 mmol/d for 8 more days. Salt-sensitivity was defined as an increase in diastolic blood pressure comparing the 10 to the 400 mmol/d intake. Salt-resistance was defined as no increase, or a decrease in diastolic blood pressure with increased Na intake. In the second protocol, 12 white and 12 black normal men ingested either 10, 200, or 400 mmol/d Na in random order each for 7 days. All urine made was collected in both protocols.

In addition to conventional statistics, a pharmacokinetic analysis was done to determine the elimination rate constant, ke and the half-life T1/2. In protocol 1, when salt intake was decreased, salt-sensitive hypertensive subjects had a longer T1/2 (2.1±0.9 vs. 1.4±0.5 days; $P \leq 0.05$) than salt-resistant hypertensive subjects. T1/2 for normotensive, salt-sensitive and salt-resistant subjects was not different (1.6±0.2 vs. 1.8±0.6 days). When salt intake was decreased, a monoexponential equation fitted the data for all subjects; when salt intake was increased, data for only half the subjects could be fitted to the same equation. In protocol 2, black race had a significant influence on UNaV ($P \leq 0.05$), in that T1/2 was prolonged in blacks compared to whites. We conclude that an increased T1/2 for Na balance may follow salt-sensitive increases in blood pressure rather than precede them. Race influences the time required to achieve salt balance. Na kinetics are not a first order process.

INTRODUCTION

Epidemiological and interventional observations suggest a relationship between dietary salt (NaCl) intake and blood pressure (MacGregor, 1985). A variety of studies have demonstrated heterogeneity of blood pressure responses to salt intake and extracellular fluid volume manipulation (Kawasaki et al., 1978; Fujita et al., 1980; Dustan et al., 1986; Campese et al., 1982; Miller et al., 1983; Koolen and van Brummelen, 1984; Skrabal et al., 1984; Weinberger et al., 1986; Sowers et al., 1988; Sullivan et al., 1988; Sharma et al., 1989; Khaw and Barrett-Connor, 1990.). This variability of responsiveness has led to the concept of salt-sensitivity and salt-resistance of blood pressure, and has been demonstrated in normal as well as hypertensive subjects. However, precisely how the connections between salt, volume, and hypertension are related to causation or correlation remains unclear (Robertson and Fraser, 1987).

Simpson (1988) discussed the relationship between salt intake, body Na, and Na excretion in terms of Na kinetics. He expanded on earlier observations dating back to Ludwig (1885) and Strauss et al. (1958). He proposed a general, monoexponential equation, which would be applicable to any change in Na intake, either positive or negative. Since altered Na kinetics could be involved in the development of hypertension in salt-sensitive individuals, we applied the kinetic approaches proposed by Simpson to data derived from salt-sensitive and salt-resistant hypertensive and normotensive, white and black subjects. The subjects ingested known amounts of salt under metabolic conditions. We determined the half-life for Na balance. We compared white and black normal subjects. Finally, we tested whether or not Na balance follows first, or zero order kinetics.

METHODS

Eighteen normal and 36 hypertensive men and women, ranging in age from 19 to 29 years for the normal and 19 to 39 years for the hypertensive subjects respectively, were invited to participate in dietary salt intervention studies performed at the Ernst-Moritz-Arndt University in Greifswald. Data on Na balance, blood pressure responses, Na accumulation, and humoral responses have been previously reported elsewhere (Wedler, 1989; Wiersbitzky et al., 1990).

In the hypertensive subjects, all medications were discontinued for a period of at least 14 days, prior to admission to the metabolic ward. The subjects remained on the ward for a 22 day period, during which time they ate a controlled diet and collected all their urine.

A basic diet providing 80 g protein, 60 mmol potassium (K) 10 mmol Na as NaCl was given daily. To this diet, either 110 mmol or 390 mmol Na as the chloride salt was added to provide 120 mmol Na or 400 mmol Na daily. The subjects received Na 120 mmol/d for 6 days. They were then given Na 10 mmol/d for 8 days, followed by 400 mmol/d for another 8 days. Compliance to the regimen was determined by observations on the ward, as well as by measurements of daily urinary Na and creatinine excretion for the 22 days. Thereafter, the subjects were discharged from the hospital. Hypertensive subjects had medical treatment resumed, if indicated.

Blood pressure was determined daily in the subjects while supine by a trained physician at the last day of the 10 mmol Na and the 400 mmol Na diets. On these days, blood pressure was measured supine every 60 min 'around the clock' with a mercury sphygmomanometer. The 5th Korotkoff sound was used to determine the diastolic pressure. From these 24 measurements, we calculated a mean systolic and a mean diastolic pressure for each subject. Salt-sensitivity was defined as an increase in the mean diastolic blood pressure comparing the measurement after 8 days of the 10 mmol/d Na diet to the value obtained after 8 days of the 400 mmol/d Na diet. Those exhibiting no change or a decrease in diastolic pressure were classified as salt-resistant. Our rationale for viewing salt-sensitivity and salt-resistance of blood pressure in this manner is detailed elsewhere (Wedler, 1989). Peripheral vascular resistance is known to normally decrease with dietary salt loading, while cardiac output increases (Simon and Levenson, 1991). An increase in diastolic blood pressure identified those subjects who failed to decrease their peripheral vascular resistance (salt-sensitive), while a decrease in diastolic blood pressure reflected those subjects who decreased their peripheral vascular resistance with salt loading (salt-resistant).

At Indiana University, 12 white and 12 black normotensive men ranging in age from 19 to 32 years were recruited to participate in a protocol to develop improved methods of determining dietary salt intake (Luft et al., 1982a). They ate all meals in the Clinical Research Center, and were otherwise free to go about their business as usual. Their diet contained 10 mmol Na, 80 mmol K, 80 g protein, 370 g carbohydrate, 400 mg calcium, and 1200 mg phosphorus daily; to this was added 190 or 390 mmol Na daily, as NaCl. Each subject ate either 10, 200, or 400 mmol Na daily for 7 days; these levels of Na intake were selected to reflect the range of NaCl intake observed in the world's populations (Intersalt Cooperative Research Group, 1988). The order of the salt intake in this study was randomly assigned. All urine made was collected. Pulse and blood pressure were measured after 5 min of rest while sitting. A mercury manometer was used by the same observers throughout the study. The 5th Korotkoff sound was accepted as the diastolic pressure.

At the Universities of Greifswald and Indiana, the protocols employed were approved by the local committees on the protection of human subjects and written consent was obtained according to the Helsinki accords.

Na was measured in urine by means of flame photometry. Creatinine in urine was determined by automated methods. Mean arterial blood pressure was calculated by adding one-third the pulse pressure to the diastolic pressure. The data were analyzed by parametric and non-parametric methods, analysis of variance, and *t* tests as appropriate by means of a computerized program (SPSS), at the University of Louisville. The 95% limits of probability were accepted as significant. The data were expressed as mean ± SD.

The pharmacokinetic analysis of the urinary Na excretion data was performed using a one compartment model with first order elimination. The form of the equation used was the one proposed by Simpson (1988) and is described as follows:

$$Na_U(t) = Na_U(t_0) + \delta Na_{In}(1 - e^{-ke}\, t)...$$

The time in days is t, $Na_U(t)$ is the urinary Na excretion at time t, $Na_U(t_0)$ is the urinary Na excretion at baseline (when t = 0), e is the base for natural logarithms, and ke is the first order rate constant. δNa_{In} is the step change in sodium intake and can carry either a positive or a negative sign. The elimination rate constant for each of the three diets in the

Indianapolis data and for the 10 and 400 mmol/d diets in the Greifswald data were determined by computer modeling the above equation to the individual data. In some cases, the data appeared to have a second compartment. Since there was not adequate data to fully describe this second, slower equilibrating compartment, we fit only data which fitted the one compartment model. The data were fitted using the nonlinear regression program PCNONLIN (Statistical Consultants Inc., Lexington, KY, USA).

Analysis of the Na excretion data was performed by means of analysis of variance using SPSS/PC+ (SPSS Inc., Chicago, IL, USA). Data from the Greifswald study were analyzed in two separate computer runs. The dependent variable UNaV was regressed against the independent variables time and group, where group represented the four subject groups (salt-sensitive normal, salt-sensitive hypertensive, salt-resistant normal, salt-resistant hypertensive). The data from the Indianapolis study was analyzed in a single computer run. The dependent variable UNaV was regressed against the independent variables diet (10, 200, 400 mmol/d), race (white, black) and time. The calculated elimination rate constant Ke was further analyzed by analysis of variance with race, diet, and time as the factors. A Newman–Keuls post-test was used to determine the order of any difference. The half life (T1/2) was calculated as: $T1/2 = 0.693/Ke$ and is expressed in days.

RESULTS

The subjects

The 18 normotensive subjects from Greifswald had a mean age of 23.1±4.4 years, and a mean body weight of 73±5 kg. Seven were classified as salt-sensitive on the basis of an increase in diastolic blood pressure (72.2±6.9 to 75.4±7.7 mm Hg) with salt loading. Eleven were classified as salt-resistant in that their diastolic blood pressure either did not change or decreased (74.7±5.2 to 68.9±7.4 mm Hg) with salt loading. The 36 hypertensive subjects had a mean age of 29.2±5.3 years and a mean body weight of 85±10 kg. Thirteen were classified as salt-sensitive on the basis of an increase in diastolic blood pressure (81.6±7.3 to 86.3±9.4 mm Hg) with salt loading. Twenty-three hypertensive subjects were classified as salt-resistant. Their diastolic blood pressures decreased (85.6±9.4 to 81.8±9.2 mm Hg) with salt loading. Urine creatinine excretion for the four groups were not different on the 10 and 400 mmol/d levels of Na intake. The total amounts of Na accumulated by the four subject groups 8 days after they were changed from a 10 to 400 mmol/d Na intake was calculated by subtracting the measured UNaV from the 400 mmol/d Na intake. These values were: salt-sensitive normal 1354±416; salt-resistant normal 1556±485; salt-sensitive hypertensive 1435±347; salt-resistant hypertensive 1596±379. There were no significant differences (ANOVA and by Kruskal–Wallis) between the groups.

In Indianapolis, mean blood pressure, body weight and urine creatinine excretion of 12 white and 12 black normotensive men were studied at three levels of Na intake, 10, 200, and 400 mmol/d and were reported earlier elsewhere (Luft et al., 1982a). The white and black men did not differ with respect to blood pressure, body weight or creatinine excretion. The diets were given in random order. Body weight was influenced significantly with differing Na intake, while mean blood pressure and creatinine excretion were not affected. Blacks and whites did not differ with respect to these variables (Luft et al., 1982a). Blacks accumulated more Na than whites ($P<0.05$) on the 400 mmol/d Na intake (385±153 vs. 909±327 mmol/Na).

Sodium kinetics

In Table 1 are shown urinary Na excretion (UNaV), Ke, and T1/2 of the salt-sensitive and salt resistant, normotensive and hypertensive subjects from Greifswald. The variables are presented in the table in chronological order; Na intake was lowered from 120 to 10 mmol/d and then increased from 10 to 400 mmol/d. With decreasing Na intake, the T1/2 of salt-sensitive hypertensive subjects was greater than for salt-resistant hypertensive subjects ($P\leq0.05$). On the other hand, the T1/2 for salt-sensitive and salt-resistant normotensive subjects was not different. With increasing Na intake, the T1/2 appeared numerically greater than with decreasing Na intake, although by paired t test no significant difference could be identified. However, the monoexponential equation could be fitted to the data for only 50, 63, 55 and 41% of salt-sensitive and salt-resistant, normotensive and hypertensive subjects, respectively. On the other hand, with decreasing Na intake all (100%) of the subjects' data could be fitted to the monoexponential equation.

In Table 2 are shown UNaV, Ke, and T1/2 of the normotensive, white and black subjects from Indianapolis. The data were analyzed by analysis of variance with UNaV as the dependent variable. The effect of Na intake, time, and race were examined. Both race and time had a significant ($P\leq0.05$) influence on UNaV.

In Fig. 1 is shown the relationship between UNaV and time (days) for all subjects at Greifswald. The diets are shown in the order in which they were

TABLE 1

Sodium excretion (UNaV), elimination rate constant (Ke), and half-life (T1/2) in salt-sensitive (SS) and salt-resistant (SR), normal (N) and hypertensive (H) subjects (mean±SD)

	120 to 10 mmol/d			10 to 400 mmol/d			
	UNaV (mmol/d)	Ke	T1/2 (days)	UNaV (mmol/d)	Ke	T1/2 (days)	UNaV (mmol/d)
Salt-sensitive normal subjects (n=7)	105±41	0.44±0.07	1.61±0.24	18±8	0.49±0.37	2.52±1.78	251±45
Salt-resistant normal subjects (n=11)	128±54	0.46±0.20	1.75±0.59	18±12	0.26±0.14	3.33±1.57	299±89
Salt-sensitive hypertensive subjects (n=13)	106±39	0.38±0.15*	2.14±0.85	16±11	0.43±0.23	2.97±1.93	283±81
Salt-resistant hypertensive subjects (n=23)	106±30	0.58±0.18	1.36±0.54	12±7	0.40±0.14	1.94±0.64	276±80

*Ke of SSH differs from the Ke of SSR ($p \leq 0.05$).

TABLE 2

Sodium excretion (UNaV), elimination rate constant (Ke), and half-life (T1/2) in white and black normal subjects receiving 10 mmol/d, 200 mmol/d, or 400 mmol/d for seven days in random order (mean±SD)*

	Whites			Blacks		
	UNaV (mmol/d)	Ke	T1/2 (days)	UNaV (mmol/d)	Ke	T1/2 (days)
10 mmol/d diet	18±3	0.74±0.26	1.08±0.45	20±4	0.65±0.34	1.65±1.29
200 mmol/d diet	168±9	0.45±0.10	1.57±0.20	172±12	0.27±0.07	2.81±0.85
400 mmol/d diet	323±21	0.28±0.10	2.88±1.50	341±26	0.21±0.10	5.81±4.79

*Data were analyzed by ANOVA, examining the effect of diet, time, and race on UNaV. Time and race were significant; further, blacks had a longer T1/2 at the 400 mmol Na intake than whites, ($p \leq 0.05$).

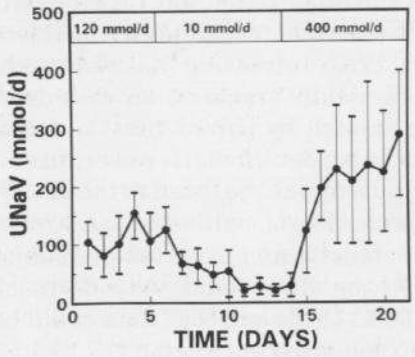

Fig. 1. The relationships between UNaV and time are shown for the subjects from Greifswald. Na 120 mmol/d was given for 6 days, followed by 10 mmol/d for 8 days, followed by 400 mmol for another 8 days.

given. In a separate analysis, no effect of salt-sensitivity, salt-resistance, or the presence of hypertension could be demonstrated on the UNaV vs. time relationship.

In Fig. 2 are shown the balance data for all subjects from Indianapolis. In the upper panel, the data are plotted as UNaV vs. time for the 200 mmol/d and 400 mmol/d diets descending to the 10 mmol/d dietary intake. In the middle panel are plotted the data from either the 10 or 400 mmol/d Na intake to the 200 mmol/d Na intake. Balance was achieved more quickly with the reduction in Na intake. In the lower panel is shown the ascent in Na intake from either 10 or 200 mmol/d to 400 mmol/d.

DISCUSSION AND CONCLUSION

The mechanisms responsible for salt-sensitive hypertension are not known. Some investigators report an accumulation of Na in the body in salt-sensitive subjects compared to their salt-resistant counterparts (Kawasaki et al., 1978; Fujita et al., 1980; Dustan et al., 1986). We were unable to show such a difference in the present study in the data from Greifswald. Interestingly, we were able to show a difference between whites and blacks, although in

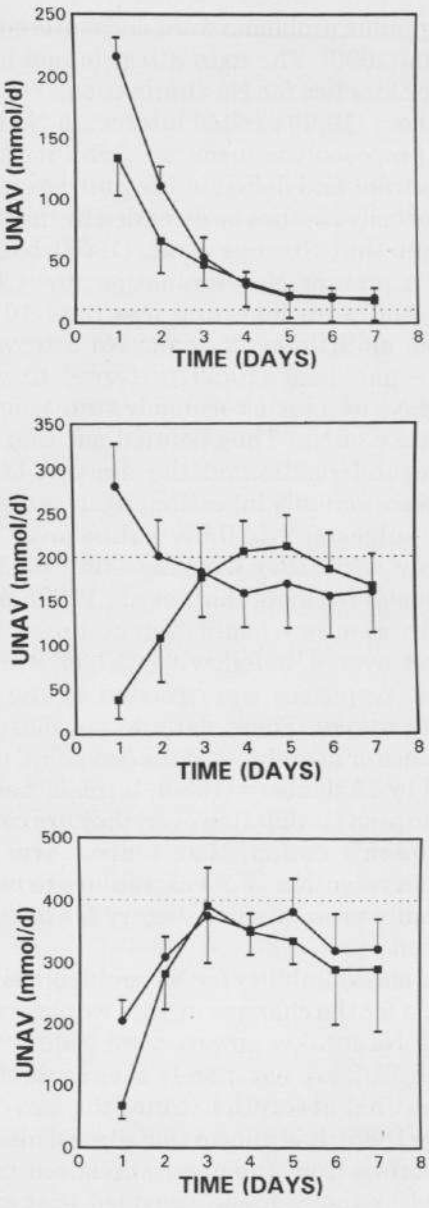

Fig. 2. Balance data for all subjects from Indianapolis. In the upper panel, the data are plotted as UNaV vs. time for the 200 mmol/d and 400 mmol/d diets descending to the 10 mmol/d dietary intake. In the middle panel are plotted the data from either the 10 or 400 mmol/d Na intake to the 200 mmol/d Na intake. Balance was achieved more quickly with the reduction in Na intake. In the lower panel is shown the ascent in Na intake from either 10 or 200 mmol/d to 400 mmol/d.

this small study of normotensive individuals, no differences in blood pressure responses to salt intake were observed. In an earlier investigation, we could not show that black subjects accumulate more Na than whites (Luft et al., 1982b), despite their greater sensitivity to blood pressure-raising effects of salt, and despite the fact that black subjects excrete a Na load more slowly over 24 h than do whites (Luft et al., 1977). The differences between the Greifswald and Indianapolis data with respect to salt accumulation raise the interesting possibility that the mechanism of salt-sensitivity may be different in whites and blacks.

We reasoned that it was nevertheless possible that salt-sensitive individuals might have a longer T1/2, reflecting a renal 'defect' in Na elimination as postulated by Blaustein and others (de Wardener and MacGregor, 1983; Blaustein et al., 1985). A longer T1/2 for older, as compared to younger normotensive subjects has been previously described (Epstein and Hollenberg, 1974). Older subjects are more likely to display salt-sensitivity than younger subjects (Khaw and Barrett-Conner, 1990). Older subjects also eliminate Na more slowly than younger subjects (Luft et al., 1980). In salt-sensitive individuals, salt-sensitivity increases in magnitude over time (Weinberger and Fineberg, 1991).

Our data show that normotensive salt-sensitive individuals have a T1/2 for Na elimination which is no different than salt-resistant normotensive subjects. Thus, a longer T1/2 for Na elimination does not appear to be a prerequisite for salt-sensitivity. On the other hand, hypertensive salt-sensitive subjects had a longer T1/2 for Na elimination compared to hypertensive salt-resistant subjects. The data are consistent with the notion that the increased T1/2 in these subjects occurred after their salt-sensitivity was established, and may be a sequel to that condition rather than a cause.

Robertson and colleagues have indicated that total body Na is increased in older hypertensive subjects, as opposed to younger hypertensive subjects, and in patients with primary aldosteronism, compared to controls (Robertson and Fraser, 1987). Total body Na is decreased in patients with renovascular hypertension. Their data indicate that the notion of a primary cause resulting in Na retention, which in turn leads to hypertension, is not likely. An alternative possibility would be that hypertension itself causes an altered relationship between total body Na and blood pressure or the manner in which Na is eliminated from the body. We could identify no difference in blood pressure between salt-sensitive normotensive and salt-resistant normotensive subjects at the basal Na intake level of 120 mmol/d. However, we did not perform 24 h blood pressure measurements at that level of Na intake; more subtle differences may have been apparent. Recently, differences in exercise blood pressure and circadian rhythm have been described between white and black men (Ekelund et al., 1990). The latter are at greater risk for the development of hypertension. They also are more likely to be salt-sensitive

(Weinberger et al., 1986). Alternative possibilities include a primary cause which results in abnormalities in electrolyte transport at the cellular level. This abnormality could result in the parallel occurrence of hypertension and altered Na elimination. Moreover, hypertension and the above cellular transport abnormality may exist in parallel and not necessarily contribute to one another. Our data could be consistent with either view.

We found that race had a significant impact on Na elimination expressed as UNaV in our normotensive subjects. This finding is consistent with earlier observations from our group, indicating differences in Na excretion following volume loading in white and black subjects (Luft et al., 1977). We were unable to demonstrate this difference in terms of a simple increase in T1/2 when dietary Na intake was abruptly reduced. However, the difference was apparent in terms of T1/2, when dietary Na intake was increased to 400 mmol/d. The Indianapolis data do not agree with the Greifswald data in that the latter showed no difference in T1/2 when salt-sensitive and salt-resistant subjects were compared. The former, on the other hand showed a prolonged T1/2 in blacks compared to whites, which is more in agreement with the notion that volume expansion may play a role in salt sensitivity. However, it is entirely possible that many mechanisms contribute to salt sensitivity of blood pressure. Those involving African-American citizens of Indianapolis may be quite different than those involving the more homogeneous citizens of Greifswald.

The second purpose of our study was to test the linearity of Na elimination. Strauss assumed that Na elimination was a first order process, i.e. T1/2 with decreasing Na intake equals T1/2 with increasing Na intake. Simpson (1988) pointed out that data to test the accuracy of the model with respect to increasing intake of Na were scant. As a matter of fact, he suggested that Na excretion to a steep increase in Na intake was probably not a simple exponential. He suggested that a delay in switching off Na retaining mechanisms, and/or switching on Na excretory mechanisms might be present. Such a delay would cause the T1/2 to be dose-related, ie. the greater the increase in Na intake, the longer the T1/2. Recently, Sagnella et al. (1990) showed that Na excretion was a first order process for decreasing Na intakes. However, this relationship was not apparent when Na intake was increased. Our data suggest that Simpson was correct in his presumption; moreover, the data are very consistent with the observations of Sagnella et al. (1990). We encountered difficulties in fitting the data to the monoexponential equation when dietary Na was increased; similar problems were encountered by Sagnella et al. (1990). The data attest to non-linear, or 'zero' order kinetics for Na elimination.

Hollenberg (1980) excited interest in Na kinetics, when he proposed the term 'set-point' for the state between surfeit and deficit in Na, and described it as the level of body Na that is 'defended by the body'. He pointed out that Strauss et al. (1958) had earlier observed a prompt Na elimination (by 4 h) when subjects, who were ingesting less than 10 mmol/d were given as little as 15 mmol Na intravenously. Bonventre and Leaf (1982) preferred to view the total body Na as a series of steady states, depending on the intake of Na. They pointed out that Strauss may have underestimated the amount of Na his subjects were actually ingesting. In an earlier study, we gave subjects 2 l, 0.9% saline over 4 h intravenously, while they were ingesting 10, 300, 600, or 800 mmol/d Na diets (Luft et al., 1983). At the 10 mmol/d intake, we could detect no significant natriuresis over 4 h following 2 l of saline. The natriuretic responses were related to the level of dietary Na intake. These data do not detract from the relevance or usefulness of the 'set point' principle described by Hollenberg (1980), termed "basal body Na" by Simpson (1988). However, they are consistent with Simpson's notion, that control over mechanisms of Na retention or Na excretion are not necessarily equally prompt when dietary Na is decreased or increased.

Altered bioavailability for Na could conceivably be responsible for the changes in T1/2 we observed with increasing Na intake; however, we believe that the changes in T1/2 are not merely the result of altered gastrointestinal absorption. Since the early studies of Ludwig (1885), it is known that almost all ingested Na is absorbed from the gastrointestinal tract and eliminated by the kidneys, provided that excessive sweating or diarrhea are not present (Earley and Daugharty, 1968). No diarrhea was observed in, or reported by our subjects. The levels of Na intake we employed are ingested by certain groups routinely (Intersalt Cooperative Research Group, 1988). We observed an altered UNaV–time relationship already with the 200 mmol/d level of Na intake.

We modeled our data assuming first order elimination. The data support this assumption. However, the data also suggest that more than one compartment may exist for Na, particularly when the Na intake is increasing. Since the data decline and/or accumulate in an exponential fashion, calculating the slope (ke) and a half-life is valid for that portion of the curve. Specifically, when Na intake is decreased the data fit a one compartment model quite well. However, when Na intake is increased,

the data appear to have a second compartment which would likely have a longer half-life. The data analysis we performed excluded the data from this second phase and is therefore descriptive of the first phase of Na accumulation during an increasing Na intake. This first phase appears to account for approximately 90% of the Na accumulation. Thus, we have adequately described 90% of Na disposition during an increasing Na diet. The final Na disposition remains to be determined; we do not have sufficient data to model this second phase.

The central compartment presumably consists of the blood plasma and other related areas of the extracellular fluid volume such as the interstitial fluid, that are in rapid volume equilibrium with the blood plasma. The second compartment may be represented by intracellular or deep tissue stores such as bone, where Na may be deposited relatively independent of changes in extracellular volume or the plasma Na concentration. Instead, Na deposition in the deep tissue compartment may lag behind extracellular Na accumulation. How such a process occurs is by no means obvious. Concentration gradients would appear unlikely; we were unable to show that marked increases in Na intake lead to any increases in the plasma concentration (Luft et al., 1982b). The data indicate that Na excretion lags behind abrupt increases in Na intake. Subsequent natriuresis may require 'filling' of the second compartment, a process which appears to require more than 3 or 4 days. After the rapid phase of equilibration a slower phase in Na excretion may ensue, requiring an unknown additional period of time until Na balance is achieved. Sagnella et al. (1990) also observed a delay in Na excretion with increased Na intake, consistent with a two-compartment model of Na elimination.

We conclude that the control mechanisms of Na homeostasis come into play at different rates when Na intake is increased compared to when it is decreased. Racial differences may exist in this regard. We can attribute no general pathogenetic importance to this phenomenon with respect to salt-sensitivity or hypertension, since salt-sensitive normotensive subjects had no increase in T1/2. However, Na elimination kinetics and their non-linearity may be of importance in non-hypertensive salt retaining states.

ACKNOWLEDGEMENTS

We thank Prof. Myron H. Weinberger (Indianapolis, IN, USA) and to Prof. Johannes F.E. Mann for their helpful comments. We are grateful to Prof. Detlev Ganten (Heidelberg, FRG) for promoting the collaboration between B. Wedler and F.C. Luft.

These studies were supported in part by Grant NO1-HV-02904 from the US Public Health Service and Grant RR 00750 General Clinical Research Center.

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