Reduced osmotically inactive Na storage capacity and hypertension in the Dahl model

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Reduced osmotically inactive Na storage capacity and hypertension in the Dahl model. Am J Physiol Renal Physiol 283: F134–F141, 2002. First published January 29, 2002; 10.1152/ajprenal.00323.2001.—Recent evidence suggested that Na can be stored in an osmotically inactive form. We investigated whether osmotically inactive Na storage is reduced in a rat model of salt-sensitive (SS) hypertension. SS and salt-resistant (SR) Dahl-Rapp rats as well as Sprague-Dawley (SD) rats were fed a high (8%)- or low (0.1%)-NaCl diet for 4 wk (n = 10/group). Mean arterial pressure (MAP) was measured at the end of the experiment. Wet and dry weights, water content, total body Na (TBS), and bone Na content were measured by dessication and dry ashing. MAP was higher in both Dahl strains than in SD rats. In SS rats, 8% NaCl led to Na accumulation, water retention, and hypertension due to impaired renal Na excretion. There was no dietary-induced Na retention in SR and SD rats. TBS was variable; nevertheless, TBS was significantly correlated with body water and MAP in all strains. However, the extent of Na-associated volume and MAP increases was strain specific. Osmotically inactive Na in SD rats was threefold higher than in SS and SR rats. Both SS and SR Dahl rat strains displayed reduced osmotically inactive Na storage capacity compared with SD controls. A predisposition to fluid accumulation and high blood pressure results from this alteration. Additional factors, including impaired renal Na excretion, probably contribute to hypertension in SS rats. Our results draw attention to the role of osmotically inactive Na storage.

MATERIALS AND METHODS

All animal experiments were done in accordance with the guidelines of the American Physiological Society and were approved by the animal care and use committee of local government authorities (AZ 621–2531.31–28/00; Regierung von Mittelfranken, Ansbach, Germany).

Animals and diets. Male Dahl rats [20 SS and 20 SR; Dahl JR strain (inbred strain), M&B, Ry, Denmark] were fed regular rat chow (0.61% NaCl) for 1 wk after arrival at our animal care facility. Then, the animals were divided into four transplanted kidney from an SS donor animal. Conversely, transplantation of SR donor kidneys into SS rats lowers blood pressure (5, 10). Despite the fact that the glomerular filtration rate is not different between both strains (2, 14), SS rats have an impaired ability to excrete Na (1, 2). However, this feature does not fully explain the development of SS hypertension (11). Thus the role of Na retention in the development of hypertension is unclear.

Recent studies on long-term Na balance in humans showed that high dietary Na consumption with Na retention does not necessarily lead to expansion of the extracellular volume (8). This finding suggests that Na might be stored in an osmotically inactive form. We studied the relationship between osmotically inactive Na storage, total body Na (TBS), total body water (TBW), and hypertension in Dahl SS rats and control animals. Our initial primary hypothesis was that Dahl SS rats exhibit a reduced capacity for osmotically inactive Na storage that would predispose these animals to volume retention and thus lead to SS hypertension. The secondary hypothesis was that osmotically inactive Na storage is also deficient in Dahl SR rats, which are genetically distinct from the Sprague-Dawley (SD) founder strain (12) and exhibit higher blood pressure than the founder strain. To determine Na and water distribution under high-dietary Na consumption, we investigated SS and SR Dahl rats (and SD rats as an additional control).
subgroups. Group 1 (10 SS, 264 ± 5.9 g) and group 2 (10 SR, 263.1 ± 10.2 g) were fed a practically NaCl-free diet (<0.1% NaCl). Group 3 (10 SS, 264 ± 10 g) and group 4 (10 SR, 263.1 ± 7.24 g) were fed a high-NaCl diet (8% NaCl) for 4 wk. Both diets contained 0.95% calcium and 0.70% potassium.

Cages and metabolic measurements. Five animals of each subgroup were kept in metabolic cages. The animals were weighed daily, and daily food and water intake as well as urine output were monitored. The remaining animals were kept in regular cages. All rats received water and food ad libitum. The cages were located in a room with constant temperature (22 ± 2°C) and humidity (60 ± 5%) and a 12:12-h light-dark cycle.

Controls. Ten male SD rats (control group 1, 248.8 ± 1.9 g) were fed a 0.1% NaCl diet. Ten SD rats (control group 2, 250.3 ± 1.6 g) were fed an 8% NaCl diet. The controls were kept in regular cages for 4 wk.

Blood pressure measurement. After 4 wk on their specified diets, the animals received intraperitoneal anesthesia with 100 mg/kg body wt methohexital, the left femoral arteries were catheterized, and blood samples were taken. Intravascular lines were connected to Statham transducers and a Gould polygraph, and blood pressure was measured 50–65 min after anesthesia, when oscillating signals occurred before complete consciousness, and then 150 min later in completely conscious animals to validate the initial measurements.

Ashing procedures. Although subtle protocols for Na balance studies in rats exist for animals fed regular chow (9), cumulative Na balance calculations are not precise enough to investigate changes in TBS during our long-term experiment. When fed a high-NaCl diet (8% NaCl), rats very often suffer diarrhea. In this case, a mixture of chow, stool, and urine with high-Na content sticks in the cages and accounts for large sampling errors. Therefore, we developed a dry ashing protocol to investigate TBS in rats. We removed both femurs and tibias and a piece of back fur from all animals for future histological and computertomographic investigations. Intestines were completely removed to exclude remains of chow. The carcasses were weighed [wet weight (WW)] and then dessicated at 90°C for 72 h [dry weight (DW)]. Because further drying left weights unchanged, we considered the difference between WW and DW as TBW

The dried carcasses were then ashed at 190 and 450°C for 24 h at each temperature level. Thereafter, we removed the skull, all cervical, thoracic, lumbar, and sacral vertebrae, 12 caudal vertebrae, the forelimb bones, and the pelvis without substantial bone ash loss. These bones were completely ashed at 700°C for an additional 24 h. Final ashing of the bone-free carcasses was performed at 600°C for 48 h. Bone ashes were dissolved in 60 ml of 10% HNO₃/sample. Carcass ashes were dissolved in 100 g of 5% HNO₃.

Electrolyte measurements. Na concentrations ([Na]) in urine and blood samples were measured with a flame photometer (model EFIX 5055; Eppendorf, Hamburg, Germany). [Na] in dissolved ashes was measured with flame photometry (model 3100, PerkinElmer, Rodgau, Germany).

Data analysis. Data are expressed as means ± SE. Mean arterial blood pressures (MAP), weights, water contents, and electrolyte concentrations were analyzed with multivariate analysis (general linear model). Post hoc tests were performed with the Bonferroni algorithm. All comparisons of means were analyzed with SPSS software (version 10.0). Curve fitting in scatterplots was done with ORIGIN software (version 6.0).

Osmotically inactive Na determination. Figure 1 gives an example of Na content and water content in rats fed a 0.1 or 8% NaCl chow. Na content [TBS(dry)] is given as millimoles per gram DW, and water content [TBW(wet)] is given as the percentage of WW. Dietary-induced Na accumulation (ΔTBS) is associated with increased body water content (ΔTBW).

To investigate the relationship between changes of Na content and alterations of water content, respectively, TBS was normalized to 1 g WW

\[
TBS_{(wet)} = TBS_{(dry)} \cdot [1 - TBW_{(\%)}; 0.01]
\]

Water volume TBW was normalized to 1 g WW

\[
TBW_{(wet)} = \frac{TBW_{(\%)}}{100}
\]

Na accumulation (ΔTBS) was defined, as shown in Fig. 1, as the difference between high-Na content [TBS(high)] and low-Na content [TBS(low)]

\[
TBS_{(high)} = (WW - DW) \cdot 100
\]

Fig. 1. Na and water accumulation (see MATERIALS AND METHODS). TBS(high) and TBS(low), total body high- and low-Na content, respectively. TBW(high) and TBW(low), total body high- and low-water content, respectively.
\[ \Delta \text{TBS} = \text{TBS}_{\text{high}} - \text{TBS}_{\text{low}} \] (4)

Water accumulation (\( \Delta \text{TBW} \)) was calculated, as shown in Fig. 1, as the difference between high-water content \( \text{TBW}_{\text{high}} \) and low-water content \( \text{TBW}_{\text{low}} \):

\[ \Delta \text{TBW} = \text{TBW}_{\text{high}} - \text{TBW}_{\text{low}} \] (5)

Increased extracellular Na content leads to water retention and therefore is considered as osmotically active Na. Assuming that \( \Delta \text{TBS}_{\text{osm}} \) is due to increased osmotically active Na \( \Delta \text{TBS}_{\text{osm}} \) in the extracellular space, this Na fraction can be estimated with the help of the plasma Na:

\[ \Delta \text{TBS}_{\text{osm}} = \Delta \text{TBW}_{\text{osm}} \left( \frac{[\text{Na}]_{\text{plasma}}}{1000} \right) \] (6)

The fraction of osmotically inactive Na \( \Delta \text{TBS}_{\text{in}} \) is

\[ \Delta \text{TBS}_{\text{in}} = \Delta \text{TBS}_{\text{osm}} - \Delta \text{TBS}_{\text{osm}} \] (7)

RESULTS

Electrolyte and water contents. Weights and calculated water contents are shown in Fig. 2. High-NaCl consumption led to stunted growth in Dahl SS (78.7 ± 5.39 vs. 128.1 ± 4.42 g DW, \( P < 0.001 \)) and SD rats (113.2 ± 4.17 vs. 123.63 ± 2.46 g DW, \( P < 0.05 \)) but not in Dahl SR rats.

When rats were fed 8% NaCl, total water content was 10% higher (69.7 ± 0.72 vs. 60.7 ± 0.84%, \( P < 0.001 \)) in SS rats and also elevated in SD rats (66.5 ± 0.30 vs. 65.07 ± 0.34%, \( P < 0.01 \)) but unchanged in SR rats. With 0.1% NaCl, water content was higher in SD than in SS rats (65.1 ± 0.34 vs. 60.7 ± 0.84%, \( P < 0.01 \)). When rats were fed 8% NaCl, water content was lower in SD than in SS rats (66.5 ± 0.30 vs. 69.7 ± 0.07%, \( P < 0.01 \)). Water content did not differ between SR and SD rats.

\( \text{TBS} \) (mmol/g DW) is shown in Fig. 2C. In SS rats, high-NaCl consumption resulted in Na accumulation (0.240 ± 0.016 vs. 0.139 ± 0.003 mmol/g, \( P < 0.001 \)), whereas \( \text{TBS} \) was unchanged in SR and SD rats.

Na content was similar in all animals fed a low-NaCl diet. When fed 8% NaCl, \( \text{TBS} \) was higher in SS than in
SR (0.172 ± 0.005 mmol/g, \( P < 0.001 \)) and SD rats (0.163 ± 0.007 mmol/g, \( P < 0.001 \)).

 electrolyte balance studies. Figure 3 shows average daily natriuresis (\( \mu \text{mol/g DW} \)) and Na intake (\( \mu \text{mol/g DW} \)). On a 0.1% NaCl diet, there was no difference in natriuresis between SS and SR rats. On an 8% NaCl diet, SR rats ingested 5.6% more NaCl than did SS rats (109.8 ± 1.43 vs. 104.0 ± 1.57 \( \mu \text{mol/g, } P < 0.01 \)). Natriuresis was 15.3% higher in SR rats (107.3 ± 1.06 vs. 93.1 ± 1.79 \( \mu \text{mol/g, } P < 0.001 \)).

 Arterial blood pressure. Figure 2D shows MAP measured 50–65 min after anesthesia, when oscillating blood pressure signals appeared. In all strains, average MAP was not different when measured 150 min later in completely conscious animals.

 Fed 0.1% NaCl, SD rats had the lowest MAP (112.2 ± 4.06 vs. 133.0 ± 3.74 mmHg in SR rats, \( P < 0.01 \), and 165.00 ± 11.95 mmHg in SS rats, \( P < 0.01 \)). On 0.1% NaCl, MAP in SR rats was lower than in SS rats (\( P < 0.05 \)).

 Fed 8% NaCl, all strains again had a different MAP. SD rats had the lowest MAP (122.8 ± 4.29 vs. 139.4 ± 4.06 mmHg in SR rats, \( P < 0.05 \), and 229.5 ± 7.69 mmHg in SS rats, \( P < 0.001 \)). On 8% NaCl, MAP in SR rats was lower than in SS rats (\( P < 0.001 \)).

 A high-NaCl diet increased MAP in the SS rats (229.5 ± 7.69 vs. 165.0 ± 11.95 mmHg, \( P < 0.001 \)) but not in the SR or SD strains.

 Na storage. Serum [Na] was 144.3 ± 0.39 mmol/l in all pooled rats (no differences between strains and diets, \( P > 0.1 \)). Increased body Na content went along with increased body water in all strains (Fig. 4A). However, the extent of Na-associated fluid accumulation showed immense variations.

 As Fig. 2C indicates, high-NaCl consumption led to true Na accumulation and water retention in Dahl SS rats. Fed 0.1% NaCl, TBS was 0.139 mmol/g DW and accompanied by 60.7% TBW. According to Eqs 2 and 3, TBS was 54.63 × 10⁻³ mmol/g WW and associated with 607 × 10⁻³ ml/g WW TBW. On high-NaCl consumption, TBS was 0.240 mmol/g DW and accompanied by 69.7% TBW. According to Eqs 2 and 3, TBS was 72.72 × 10⁻³ mmol/g WW and TBW was 697 × 10⁻³ ml/g WW. According to Eqs 4 and 5, \( \Delta \text{TBS} \) was 18.09 × 10⁻³ mmol/g and coincided with 90 × 10⁻³ ml/g \( \Delta \text{TBW} \) in SS rats. On the assumption that water retention was due to increased extracellular Na content, osmotically active Na retention was 12.99 × 10⁻³ mmol/g (6). Thus osmotically inactive Na retention was 5.10 × 10⁻³ mmol/g (7).

 Dietary Na loading did not increase average Na content in SR and SD rats (Fig. 2C). Thus \( \Delta \text{TBS} \) calculations, including determination of \( \Delta \text{TBS}_{(a)} \) and \( \Delta \text{TBS}_{(i)} \) on the basis of intraintrain Na content differences due to dietary Na loading, were not possible in both strains. However, independent of the dietary regime, Dahl SR as well as SD rats showed marked intragroup variations in Na and water content (Fig. 4A) that allowed such calculations in both strains. As curve fitting indicates, increased Na content was associated with increased water content in SR and SD rats. We plotted these correlations but wanted to avoid calculations on the basis of curve fits alone. Therefore, we stratified the data from each rat strain for TBS so that the 10 rats with the highest TBS constituted one group (high) and the other 10 rats made up the second group (low). The intraintrain differences of TBW and MAP between both groups were then tested with variance analysis.

 In SR rats, low TBS was 0.147 mmol/g DW and high TBS was 0.179 mmol/g DW. Low TBS was associated with 62.1% TBW, whereas high TBS coincided with 65.4% TBW (\( P = 0.01 \)). Normalized to 1 g WW (2–5), \( \Delta \text{TBS} \) was 6.22 × 10⁻³ mmol/g, whereas \( \Delta \text{TBW} \) was 33 × 10⁻³ ml/g. Thus, in Dahl SR rats, the fraction of osmotically active Na was 4.76 × 10⁻³ mmol/g (6). The fraction of osmotically inactive Na was 1.46 × 10⁻³ mmol/g (7).

 In SD rats, low TBS was 0.143 mmol/g DW and high TBS was 0.180 mmol/g DW. Low TBS was associated with 64.9% TBW, whereas high TBS coincided with 66.6% TBW (\( P < 0.01 \)). Normalized to 1 g WW (2–5), \( \Delta \text{TBS} \) was 9.93 × 10⁻³ mmol/g, whereas \( \Delta \text{TBW} \) was 17.0 × 10⁻³ ml/g. Thus, in SD rats, the fraction of

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Fig. 3. A and B: average daily natriuresis and Na intake in SS and SR Dahl rats, respectively. W1–W4, weeks 1–4. ††\( P < 0.01 \), †††\( P < 0.001 \).

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osmotically active Na was $2.45 \times 10^{-3}$ mmol/g (6). The fraction of osmotically inactive Na was $7.48 \times 10^{-3}$ mmol/g (7).

Respectively, the amount of osmotically inactive Na accumulation was 28.2% in SS and 23.5% in SR but 75.3% in the SD strain (Fig. 4B).

Na and water content and their association with blood pressure. Body Na content and blood pressure in individual rats were correlated significantly in all strains (Fig. 4C). Again, the slope of the Na content/blood pressure curve differed between strains. In SS rats, Na accumulation from 0.139 to 0.240 mmol/g increased MAP by 64.5 mmHg, from 165 to 229.5 mmHg ($P < 0.001$). In SR rats, increased TBS from 0.147 to 0.179 mmol/g increased MAP from 130 to 143.1 mmHg ($P = 0.01$). In SD rats, TBS elevation from 0.143 to 0.180 mmol/g increased MAP from 111.2 to 124.1 mmHg ($P < 0.05$). Respectively, a 0.01 mmol/g TBS increase elevated MAP by 6.4 mmHg in SS rats, 4.1 mmHg in SR rats, and 3.5 mmHg in the SD strain.

Increased body water content was associated with increased blood pressure in all strains (Fig. 4D). The extent of volume-associated hypertension showed different strain specificity. In SS rats, increased water content from 60.7 to 69.7% increased MAP from 165 to 229.5 mmHg. In SR rats, increased water content from 62.2 to 65.4% increased MAP from 130 to 143.1 mmHg. In SD rats, TBW elevation from 64.9 to 66.6% increased MAP from 111.2 to 124.1 mmHg. Respectively, TBW expansion by 1% was associated with 7.2 mmHg blood pressure increase in SS rats and 7.6 mmHg in SD rats. In SR rats, the effect of elevated water content was small. One percent increases in TBW were associated with only a 4.1-mmHg blood pressure increase.

Bone Na contents. Bone Na can be regarded as a potent osmotically inactive Na compartment. To investigate its contribution to TBS(i), we determined the bone Na content in the rats.

With regard to low-salt diets, bone Na content per gram of rat DW was similar in both strains of Dahl rats.
but higher than in SD rats \( (P < 0.05 \text{ and } < 0.001, \text{ respectively; Fig. 5A}) \). In rats fed 8\% NaCl, SR and SD bone Na did not differ significantly, whereas bone Na content in SS was higher \( (P < 0.001) \). Within groups of rats, high dietary NaCl consumption coincided with elevated skeletal Na contents in SS \( (39.9 \pm 1.90 \text{ vs. } 27.8 \pm 1.55 \mu\text{mol/g}, P < 0.001) \) and also in SD rats \( (27.7 \pm 1.61 \text{ vs. } 24.8 \pm 1.38 \mu\text{mol/g}, P < 0.001) \) but not in SR rats. Similar to TBS, in SR rats bone Na content showed large variations that were independent from the diet. Increased TBS increased bone Na in all rats \( \text{Fig. 5C} \).

Having found that high-NaCl consumption led to TBS as well as bone Na accumulation, we calculated the bone Na-to-TBS (Na/TBS) ratio to investigate Na distribution in the body \( \text{Fig. 5B} \). Increasing TBS from 0.139 to 0.240 mmol/g in Dahl SS rats fed 8\% NaCl, they had a reduced bone Na/TBS ratio \( (0.197 \pm 0.004 \text{ vs. } 0.171 \pm 0.006 \mu\text{mol/g}, P < 0.01) \). In Dahl SR or SD rats, high-NaCl consumption left the bone Na/TBS ratio unchanged. However, TBS increases that were independent of diet influenced the bone Na/TBS ratio in SR rats \( \text{Fig. 5D} \). Similar to SS rats, increased TBS correlated with a reduced bone Na/TBS ratio in SR rats. In SD rats, increased TBS did not significantly change the bone Na/TBS ratio \( \text{data not shown} \).

Body Na distribution was different in SD rats compared with both Dahl strains. On 0.1\% NaCl, only 16.0 \pm 1.2\% of TBS was found in bones of SD rats compared with 19.6 \pm 2.5\% in SR rats, \( P < 0.01 \), and 19.7 \pm 0.13\% in SS rats, \( P < 0.01 \). Relative bone Na contents were not different between the strains fed high-NaCl diets.

Na distribution and its association with fluid volume and blood pressure. A high-NaCl diet led to Na redistribution in SS, but not in SR and SD, rats. In SS rats, 8\% NaCl reduced the bone Na fraction of TBS \( \text{Fig. 5B} \). Such Na-altered distribution in the SS strain was associated with parallel changes in fluid volume and blood pressure \( \text{Fig. 6} \). Decreased relative bone Na content observed in individual SS rats under different dietary regimes was associated with body fluid expan-
sion and increased MAP. In SR and SD rats, there was no correlation between relative bone Na content and body fluids or blood pressure (data not shown).

**DISCUSSION**

High dietary NaCl consumption led to Na retention in SS rats but not in SR and SD strains. These findings confirm the data from Tsunooka and Morita (15) in Iwai Dahl inbred strains, whereas Schackow and Dahl (13) originally reported that a high-salt diet had no effect on TBS in SS rats but did affect TBS in SR rats. Our data also confirm the finding that differences between Dahl strains are characterized by a reduced ability to excrete Na loads in SS rats (1, 2), with subsequent Na accumulation and hypertension. Although Na accumulation increased bone Na by ~43% (Fig. 3A), skeletal Na storage capacity was inadequate to cope with Na overload in SS rats. This state of affairs led to an altered Na distribution between bone and extracellular space in these rats. Furthermore, salt-induced volume expansion led to elevated blood pressure in SS rats compared with the SR strain. This observation points to the previously reported (7, 11) notion that, in addition to altered salt-induced volume expansion, volume-independent aspects contribute to the development of Dahl SS hypertension.

Irrespective of NaCl consumption, TBS in individual SR and SD rats showed large variations. The reason for these different Na contents is not clear. The elevated Na contents were correlated with increased TBW in each strain. The relationship between Na and water was strain specific. The fraction of osmotically inactive Na in SD rats was threefold higher than in Dahl SS and SR rats, as judged by the relationship between body Na and body water. We conclude that compared with SD rats, both SS and SR Dahl strains are characterized by impaired storage of osmotically inactive Na. Presumably, the Dahl rats react to increased TBS with expansion of the extracellular space. Fluid volumes consecutively rose to levels higher than those in SD rats.

Bone could be viewed as a potential osmotically inactive Na reservoir (3, 4). In all strains, increased TBS led to increased bone Na content. As indicated by an inverse correlation between TBS and the bone Na/TBS ratio (Fig. 5, B and D), in both Dahl strains (with their reduced osmotically inactive Na storage capacity), increased TBS not only increased bone Na but also changed Na distribution in favor of Na compartments other than bone. Dahl SS rats additionally had a reduced ability to excrete Na that led to Na and water excess in these animals if they were fed a high-NaCl diet. This Na and water excess in SS rats was characterized by bone Na excess. Dahl SS rats fed 8% NaCl suffered a 0.1 mmol/g TBS increase (Fig. 2C and 5A), indicating that 12% of the Na accumulated had been stored in this osmotically inactive Na compartment. Because the fraction of osmotically inactive Na accumulation was 28.2% (Fig. 4B), we conclude that bone is not the only osmotically inactive Na reservoir in SS rats. Such osmotically inactive Na reservoirs might function as a buffer that receives Na from a Na-overloaded extracellular space. We speculate that Na storage in an osmotically inactive compartment could be an alternative pathway for Na clearance from the extracellular space when Na loads are excessive or renal Na excretion is inadequate. Such a mechanism could reduce volume expansion and hypertension in Na-overloaded organisms. However, the mechanism is apparently inadequate to cope with the impaired renal Na excretion. In SD rats, the role of bone as a Na reservoir that osmotically inactivates extracellular Na is less readily apparent. Although these rats demonstrated the highest capacity to store osmotically inactive Na, the bone Na was lowest in SD rats. These findings suggest that other Na reservoirs in addition to bone, such as cartilage and mixed connective tissue, may be operative.

In the Dahl model, SR rats are considered the normotensive strain compared with SS rats. Apparently, renal Na handling abnormality led to Na and blood pressure excess in SS rats. Presumably, impaired renal

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**Fig. 6.** Bone Na/TBS ratio and its association with water content (A) and blood pressure (B) in SS Dahl rats. *P < 0.05, **P < 0.01.
Na excretion is associated with increased sympathetic nerve activity (16) in SS rats. Thus, besides Na and water retention, increased sympathetic nerve activity and its impact on the cardiovascular system may be an important factor in Dahl SS hypertension.

However, compared with SD rats, from which both Dahl strains were originally inbred, both SS and SR strains exhibited higher blood pressure. Even if animals were fed an NaCl-free diet, MAP in SS and SR strains was higher than in SD rats (Fig. 2). Although MAP was different, TBS in Dahl SR and SD rats, whether they were fed 0.1 or 8% NaCl, was comparable to TBS in SS rats fed 0.1% NaCl. Thus factors other than Na retention must explain the somewhat higher blood pressure in SS and SR rats compared with SD rats.

In contrast to our initial hypothesis, salt resistance in Dahl SR rats could not be explained by a higher capacity than in SS to store Na as osmotically inactive. Similar to SS rats, high-TBS levels led to exaggerated water content in the SR strain. Consequently, SR rats appear to be “water resistant” or “volume resistant.” The relationship between ΔMAP and ΔTBW was quite similar in SS and SD rats. In contrast, increased ΔTBW from 58 to 68% left blood pressure almost unchanged in SR rats (Fig. 4D). To the extent that ΔTBW reflects changes in extracellular volume and cardiac output, the lack of an increase of blood pressure points to lower peripheral resistance in SR. The lack of an increase of cardiac output measurements, we can only speculate that lower peripheral resistance might be an inbred, advantageous adaptation in SR rats rather than another disadvantage in the SS strain.

Similar to SS rats, increased water content correlated with blood pressure in SD rats (Fig. 4D), indicating a body water-blood pressure relationship comparable to that in Dahl SS rats. However, because of osmotically inactive Na storage, water content increases did not exceed 6% of WW in SD rats. We conclude that osmotically inactive Na storage is an important mechanism to buffer volume and blood pressure in SD rats. The contribution of osmotically inactive Na to Na balance has been the focus of recent studies in humans (8). The variation and amount of osmotically inactive Na in SD rats fit well with similar findings in healthy men (in humans during a terrestrial space station simulation study; Titze J, Lang R, and Kirsch KA, unpublished observations). The role of osmotically inactive Na storage should be taken into account in the pathophysiological approach to volume expansion and hypertension.

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