Pressure-dependent renin release: effects of sodium intake and changes of total body sodium

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Seeliger, Erdmann, Katrin Lohmann, Benno Nafz, Pontus B. Persson, and H. Wolfgang Reinhardt. Pressure-dependent renin release: effects of sodium intake and changes of total body sodium. Am. J. Physiol. 277 (Regulatory Integrative Comp. Physiol. 46): R548–R555, 1999.—The impact of sodium intake and changes in total body sodium (TBS) for the setting of pressure-dependent renin release (PDRR) was studied in freely moving dogs. An aortic cuff allowed servo control of renal perfusion pressure (RPP) at preset values. Protocols were 1) high sodium intake (HSI), 2) low sodium intake (LSI), 3) TBS moderately increased (+3.1 mmol Na/kg body wt) by 20% reduction of RPP for 2–4 days, 4) large increase of TBS (+8.2) by combining protocol 3 with aldosterone infusion, and 5) TBS reduced (−3.1) by peritoneal dialyses. Twenty-four-hour-time courses of arterial plasma renin activity (PRA) revealed that LSI increased PRA for the first 10 h only; afterward PRA did not differ between LSI and HSI. Reduced TBS increased PRA constantly, and the large increase of TBS constantly reduced PRA. PDRR stimulus-response curves (assessed 20 h after last sodium intake) revealed an exponential relationship in each protocol. PDRR was not changed by different sodium intake. Conversely, reduced TBS increased PDRR markedly, whereas the large increase of TBS suppressed it. Thus an inverse relationship between TBS and PRA, i.e., a TBS-dependent renin release, was found. This relationship was enhanced by decreasing RPP. This interplay between TBS-dependent renin release and PDRR allows the organism a differentiated reaction to changes in TBS and arterial pressure.

blood pressure; renin-angiotensin system; renal circulation; plasma renin activity; diurnal pattern

THE RENIN-ANGIOTENSIN-ALDOSTERONE system (RAAS) is a major factor in regulating renal Na and water excretion, and therefore in maintaining total body sodium (TBS) and total body water (TBW). The RAAS, furthermore, maintains mean arterial blood pressure (MABP) both by controlling TBW and by the vasoconstrictor action of ANG II. It is therefore not surprising that MABP as well as Na and water homeostasis impinge on one of the key elements of the RAAS, i.e., renal renin release.

It is well established that renin release is controlled by a “baroreceptor-like mechanism” (Skinner 1964, Ref. 28); renin release increases when renal perfusion pressure (RPP) decreases. This inverse relationship was quantitatively described in conscious dogs by Fahri et al. (8) and Finke et al. (10). They assessed stimulus-response curves, relating RPP to renin release or systemic plasma renin activity (PRA).

Renin release, moreover, is also controlled by renal sympathetic nerve activity and circulating catecholamines. Thus various physiological stimuli may influence renin release, including reflexes activated by atrial or arterial pressure changes (15, 30) as well as physical activity and stress (17, 20). The interaction of sympathetic activity and pressure-dependent renin release (PDRR) was quantitatively described by Kirchheim and colleagues (5, 15).

Finally, PRA is inversely related to Na intake. Although low sodium intake (LSI) is generally held to increase PRA, the pathway by which the amount of Na ingested is signaled to the renin producing cells is still under debate. A study by Fahri et al. (8) aimed to clarify whether the pressure dependence of renin release is altered by Na intake. The results were interpreted such that “a reduction in salt intake increases the sensitivity of the renal baroreceptor.” The dogs studied were fed a low-sodium diet; however, an unknown amount of Na had also been withdrawn by means of diuretics. Thus the results reported by Fahri et al. (8) might reflect the influence of a deficit in TBS rather than of LSI per se. Therefore, the primary goal of the present study was to compare the effects of changes in Na intake per se vs. surplus and deficit of TBS on the relationship between RPP and PRA.

The second goal of the study was to test whether the diurnal pattern of PRA is altered by changes in Na intake as well as by surplus or deficit of TBS. As we have recently reported (4), there is a characteristic diurnal pattern of PRA in freely moving dogs during high sodium intake (HSI). Part of the diurnal pattern, e.g., postprandial decrease of PRA (13), is assumed to be related to Na and water intake.

METHODS

Thirty-four chronically instrumented female beagle dogs, ~2 yr of age, weighing 12–19 kg, were studied by the use of standardized methods established by our laboratory, which are described in detail in previous papers (3, 21, 24). The study was approved by the Berlin Government according to the German Animal Protection Law.

Surgery and Maintenance

Each dog was equipped with a urinary bladder catheter, an inflatable cuff placed around the aorta above the renal arteries, and two femoral artery catheters. One catheter was advanced into the abdominal aorta just below the renal arteries; the tip of the other catheter was placed well above the renal arteries. All lines were exteriorized in the nape region. The dogs were allowed at least 3 wk to recover. Catheter-related infections were prevented by a catheter-
restricted antibiotic-lock technique (19). Daily checkups for
general status, body temperature, weight, and tests of erythro-
cyte sedimentation rate were performed. The dogs were
housed individually in kennels (9 m²) in a sound-protected,
air-conditioned animal room. A light-dark cycle of 12:12 h was
applied (lights on from 0700 to 1900, transition period 15
min). Physical activity was observed by means of video
cameras (infrared light during dark). For reasons of social
well-being, another dog in an adjacent kennel accompanied
the dog under investigation.

Dietary Regimen
At least 5 days before and throughout the studies, food
intake was controlled with regard to daily feeding time,
duration of intake, and food composition. The food provided
either 5.5 mmol of Na (HSI) or 0.5 mmol of Na (LSI), 3.5 mmol
of K, and 91 ml of water per day per kilogram of body weight
(i.e., 82.0 or 7.5 mmol of Na, 52 mmol of K, and 1,365 ml of
water per day to a 15-kg dog). The dogs were offered the food
once daily at 0830. In case a dog did not finish its meal within
20 min, the remainder was tube-fed to guarantee complete
food and water intake. No additional feeding and no further
access to water were allowed until feeding on the next day.

Experimental Setup
During the study, the lines of the dogs were connected to a
swivel system that allowed free movement within the limits of
the 9-m² kennel (for details see Ref. 3). The dogs were well
acclimated to this equipment. From the swivel the lines led
to the adjoining room (laboratory) via a covering tube. Hence
all actions necessary to conduct the experiments were taken
at the laboratory without drawing the attention of the dogs in
the sound-protected animal room, except for 1 h/day (0800–
0900). This time was needed for animal care, feeding, and
recalibration of the electronic systems. MABP (catheter above
the aortic occluder) and RPP (catheter below the aortic
occluder) were measured with pressure transducers inte-
grated into the swivel. Urine was collected by means of a
computerized collection system (22). Within this setup, dogs
were studied for 1–4 days.

Examination period. This lasted 24 h (0800–0800), during
which the diurnal pattern of PRA as well as the stimulus-
response curve relating RPP and systemic PRA were ob-
tained. Depending on the respective protocol, the examina-
tion period was performed either on day 1 or day 2 or day 4 of
the study.

Diurnal pattern study. This lasted from 0800 through 0400.
Blood samples were taken at 0900, 1300, 1700, 2100, 0100,
and 0400 via the arterial catheter. The withdrawn volume
was always replaced by an equal amount of blood that had
been collected from the respective dog ~2 wk before the
experiments. Each sample was analyzed for PRA, concentra-
tion of atrial natriuretic peptide (ANP), and sodium concen-
tration (Na⁺).

Stimulus-response curve study. For two reasons, the stimu-
lus-response curve of RPP and systemic PRA was assessed at
0400–0700. First, at this time, the dogs’ physical activity was
low (dark period). Second, the dogs were fed once daily at
0830–0900. Thus the relationship was studied in the postab-
sorptive state, i.e., possible postprandial interferences was
excluded. For assessment of stimulus-response curves, RPP
was servo-controlled on preset levels by inflating and deflat-
ing the aortic occluder (21). Each preset level was maintained
for a 20-min period, at the end of which a blood sample was
taken for PRA analysis. First, RPP was reduced stepwise
(each step ~10 mmHg), the lowest level being 60 mmHg.

Afterward it was stepwise released again until RPP matched
the individual dog’s MABP again.

Experimental Protocols
Five protocols were performed. The dogs were assigned the
protocols at random.

Protocol 1 (HSI). Dogs (n = 10) were on HSI. For comparabil-
ity with protocols 4 and 5, the examination period was
performed either on day 1 (n = 4) or on day 4 (n = 6) of the
study.

Protocol 2 (LSI). Dogs (n = 6) were on LSI. For comparabil-
ity, the examination period was performed either on day 1
(n = 3) or on day 4 (n = 3) of the study.

Protocol 3 ([TBS]). Dogs (n = 8) were on HSI. To induce a
moderate surplus in TBS, a continuous servo-controlled
reduction of RPP (rRPP) was performed for 2–4 consecutive
days. As described by Reinhardt et al. (21), rRPP was servo-
controlled at 80% of the individual dog’s MABP during control
days. Thereby sodium was retained on day 1, increasing TBS
by ~3 mmol Na/kg body wt. Despite further servo control,
there was no further significant increase of TBS on the
following days (21). Thus the examination period was per-
formed either on day 2 (n = 6) or on day 4 (n = 2) for
comparability with protocol 4.

Protocol 4 ([|TBS]). Dogs (n = 4) were on HSI. To induce a
large surplus in TBS, rRPP (as in protocol 3) was combined
with continuous low-dose infusion of aldosterone (Aldocorten,
Ciba, Switzerland; 10 pg·kg body wt
−1 ·min
−1) for 4 consecu-
tive days. As described by Seeliger et al. (24), sodium is
continuously retained, increasing TBS by ~9 mmol/kg body
wt. Thus the examination period was performed on day 4 of
the study.

Protocol 5 ([|TBS]). Dogs (n = 6) were on LSI. To induce a
deficit in TBS, a peritoneal dialysis was performed on day 1
at 0900 as described by Behrenbeck et al. (1). Briefly, a stylect
was inserted into the peritoneal cavity under local
anesthesia. One thousand milliliters of 5% glucose solution
(37°C, +4 mmol K) were instilled within 10 min, the catheter
was left in place for 40 min, and then the dialysate (exactly
1,000 ml) was drained. Immediately after the catheter was
drawn, the dog was connected to the experimental equip-
ment, it was fed (LSI), and the examination period took place.
Na concentration of dialysate was measured, and the amount
of Na withdrawn was calculated. In case more than 3.5 mmol
Na/kg body wt had been withdrawn, the respective difference
was calculated, and the amount of NaCl needed to match the
deficit of 3.5 mmol Na/kg was added to the food.

Analyses, Calculations, and Statistics
PRA and ANP were measured with commercially available
RIAs as described earlier (21). Na concentrations in plasma
and urine were measured by flame photometry. The urine
collected during a 24-h period was analyzed for Na concentra-
tion. Urine volume was measured by weighing. Twenty-four-
hour balances as well as cumulative balances for Na and
water were calculated for the individual dog as described ear-
erly (24). Changes in cumulative balances reflect changes in
TBS and TBW.

RPP was recorded as 1-min averages. For the assessment
of individual stimulus-response curves, the respective step’s
20-min mean RPP was calculated. RPP was first reduced
stepwise and afterward released stepwise. It was analyzed in
each experiment whether the PRA values measured on the
respective RPP steps during the reduction compared with the
increase would show any systematic variation (hysteresis).
Because no hysteresis was found, the arithmetic mean of the
respective step's two PRA values was used to assess the individual dog's curve.

The dogs were examined at different days of the study period within protocols 1, 2, and 3 (see Experimental Protocols). Because the results obtained within the respective protocol did not differ with regard to the respective day of examination, mean values were calculated for these protocols regardless of the respective day of examination.

Mean values were calculated for PRA, ANP, and PNa in dogs during high sodium intake (HSI, n = 3) and low sodium intake (LSI, n = 6). Differences between the groups were assessed by unpaired t-test with Bonferroni's adjustment for multiple comparisons, with a significance level of P < 0.05/m, where m is the number of comparisons between groups. Data are given as means ± SE.

RESULTS

Twenty-Four-Hour Balances and Changes of TBS and TBW

HSI and LSI. The dogs were fed their respective diet for at least 5 days before the study, and 24-h balances during the study were equilibrated. Dogs on HSI renally excreted 4.94 ± 0.27 mmol Na/kg body wt out of the 5.5 mmol/kg fed (mean extrarenal loss: 0.56 mmol/kg). Dogs on LSI renally excreted 0.44 ± 0.06 mmol Na/kg body wt out of the 0.5 mmol/kg fed (mean extrarenal loss: 0.06 mmol/kg). In contrast to equilibrated Na balances of dogs, which had been on their diet for several days, balances are known to be temporarily positive immediately after a step decrease in Na intake (26). To determine a possible difference of TBS between HSI and LSI, balances were obtained in six dogs during a step change from HSI to LSI. On the first day of LSI, Na balance was negative; on the second day, it was equilibrated, yielding a cumulative Na balance of −0.30 ± 0.20 mmol/kg body wt (cumulative water balance: 1 ± 4 ml/kg).

TBS. Continuous 20% reduction of RPP during HSI induced Na and water retention for ~24 h (positive 24-h balances). Although reduction of RPP was maintained on the following days, 24-h balances equilibrated; i.e., the initial surplus of TBS and TBW was not further increased nor reduced. Thus there was a surplus in TBS of 3.1 ± 0.2 mmol Na/kg body wt and a surplus in TBW of 26 ± 3 ml/kg body wt during the examination period.

TBS. By means of peritoneal dialyses, exactly 3.5 mmol Na/kg body wt were withdrawn. Immediately after dialyses, the dogs received their meal (LSI). Out of the 0.5 mmol Na/kg ingested, the dogs retained ~0.4 mmol/kg. Within the first ~20 h after dialyses, the dogs had a negative water balance. Thus there was a deficit in TBS of 3.1 ± 0.05 mmol Na/kg body wt and a deficit in TBW of 10 ± 2 ml/kg at the time of the stimulus-response study.

Diurnal Pattern of PRA

HSI. PRA was highest at 0900 (~5 ng ANG l·h⁻¹·ml⁻¹), but PRA decreased postprandially to ~1.5 ng ANG l·h⁻¹·ml⁻¹ (Fig. 1). Toward 2100, PRA reached ~2.5 ng ANG l·h⁻¹·ml⁻¹, where it remained constant until 0400.

LSI. PRA peaked at 0900 (~12 ng ANG l·h⁻¹·ml⁻¹; Fig. 1). Compared with PRA values obtained from 2100 through 0400, PRA was not lowered postprandially. Thus PRA values at 0900, 1300, and 1700 were higher during LSI than during HSI. In contrast to HSI, there was no increase of PRA toward 2100. Hence PRA values at 2100–0400 during LSI (~3 ng ANG l·h⁻¹·ml⁻¹) were not significantly different from those during HSI.

TBS. Under the conditions of RPP during HSI, PRA values were ~16 ng ANG l·h⁻¹·ml⁻¹ at 0900 (Fig. 2). Postprandial decrease did not reach the low PRA level.

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**Fig. 1.** Diurnal pattern of arterial plasma renin activity (PRA) in dogs during high sodium intake (HSI, n = 10) and low sodium intake (LSI, n = 6). Values are given as means ± SE. For points with missing error bar, SE is smaller than symbol size. For significance see RESULTS. Note that stimulus-response curve study was started immediately after 0400.
found during HSI (PRA values at 0900 and 1300 during rRPP were significantly higher). From 1700 through 0400, there were no PRA differences between these protocols.

↑TBS. PRA values were low throughout the study. PRA was \(-1.2\, \text{ng Ang I·h}^{-1}·\text{ml}^{-1}\) at 0900 (Fig. 2). Afterward it was further suppressed, being lower than 0.5 ngAng I·h\(^{-1}·\text{ml}^{-1}\) from 1300 through 0400. Hence all values were significantly lower during ↑TBS than during HSI as well as during ↑TBS.

↑TBS. Peritoneal dialysis was performed from 0900 to 1000. At first blood sampling after dialyses (1300), PRA was \(-26\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\) (Fig. 2). Until 2100 it decreased to levels of \(-11-14\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\). Thus PRA during ↑TBS was significantly higher than during HSI as well as LSI from 1300 through 0400.

Relationship Between RPP and PRA

In each protocol, when RPP was stepwise reduced an exponential increase in PRA was found in each individual dog. There was an inverse relationship between RPP and PRA even in the RPP range >90 mmHg. Thus each dog's stimulus-response curve was best fitted to an exponential function [general equation: \(\log\text{(PRA)} = (a_1 × \text{PRA}) + a_0\)], with a range of correlation coefficients of 0.88–0.99.

HSI. Mean stimulus-response curve revealed an exponential relationship \(\log\text{(PRA)} = (-0.024 × \text{RPP}) + 3.05; r = 0.995\) (Fig. 3). At \(-60\, \text{mmHg}\), the lowest RPP studied, PRA was \(-44\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\). At \(-100\, \text{mmHg}\), PRA was \(-5\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\). The individual dog's spontaneous MABP ranged from \(-100\) to \(-120\, \text{mmHg}\). Therefore, at the RPP range above \(-100\, \text{mmHg}\), PRA \(-2\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\) was only measured in 3 dogs.

LSI. Mean stimulus-response curve was \(\log\text{(PRA)} = (-0.020 × \text{RPP}) + 2.80; r = 0.986\) (Fig. 3). Mean PRA was \(-59, -5, -4\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\) at 60, 100, and \(-120\, \text{mmHg}\) (at \(-120\, \text{mmHg}\) n = 4), respectively. Mean stimulus-response curves during LSI and HSI were similar. Mean PRA was significantly higher during LSI at \(-60\, \text{mmHg}\) only. Thus LSI did not significantly enhance pressure dependence of PRA. Accordingly, the coefficients of logarithmic functions \(a_1, a_0\) were not significantly changed compared with those of HSI.

↑TBS. Mean stimulus-response curve was \(\log\text{(PRA)} = (-0.027 × \text{RPP}) + 3.10; r = 0.987\) (Fig. 4). Mean PRA was \(-36\) and \(-3\, \text{ng ANG I·h}^{-1}·\text{ml}^{-1}\) at \(-60\) and \(-100\, \text{mmHg}\), respectively. Compared with HSI, the pressure dependence of PRA was slightly reduced. However, PRA was significantly lower at \(-90\) and \(-70\, \text{mmHg}\) only, and the coefficients of logarithmic functions were not significantly changed.

↑TBS. Mean stimulus-response curve was exponential \(\log\text{(PRA)} = (-0.027 × \text{RPP}) + 2.35; r = 0.940\) (Fig. 4), but it was flattened considerably. At all RPP steps studied, PRA during ↑TBS was significantly lower than that of ↑TBS. Moreover, the lower the RPP was, the greater the difference in PRA became. In other
words, the pressure dependence of PRA was almost completely suppressed. Accordingly, the $a_0$ coefficients of the logarithmic functions were significantly less than those of HSI and TBS functions.

**TBS.** Mean stimulus-response curve was $\log (\text{PRA}) = (-0.015 \times \text{RPP}) + 2.80; r = 0.983$ (Fig. 4). The curve is well above that during HSI as well as LSI; i.e., PRA was significantly higher at any RPP studied. At $\sim 100$ mmHg, mean PRA was $\sim 17$ and $\sim 5$ ANG I·h$^{-1}$·ml$^{-2}$ during TBS and HSI, respectively. At $\sim 60$ mmHg, mean PRA was $\sim 77$ and $\sim 44$ ANG I·h$^{-1}$·ml$^{-2}$ during TBS and HSI, respectively. Thus the curve was shifted upward, and its steepness was slightly increased. The $a_0$ coefficients of the logarithmic functions were significantly less negative than those of HSI and LSI.

**MABP, Plasma ANP, and PNa**

Twenty-four-hour mean values of systemic MABP did not differ significantly between HSI (118.4 ± 2.6 mmHg) and LSI (116.0 ± 3.1). Compared with HSI, MABP increased significantly during TBS (140.3 ± 2.4 mmHg) as well as during TBS (142.4 ± 4.9 mmHg; not different from TBS). During TBS, MABP was 111.6 ± 2.1 mmHg, which is significantly lower than HSI yet not significantly different from LSI.

ANP did not reveal a clear-cut diurnal profile. Therefore, mean values for each dog were calculated out of the six values obtained during the diurnal pattern study. Mean ANP did not differ significantly among HSI (39.1 ± 2.9 pg/ml), LSI (37.0 ± 3.8 pg/ml), and TBS (35.0 ± 3.5 pg/ml). Compared with HSI, ANP increased significantly during TBS (140.0 ± 17.9 pg/ml) as well as during TBS (135.3 ± 23.3 pg/ml; not different from TBS).

PNa did not reveal a clear-cut diurnal profile in protocols 1, 2, 3, and 4. Therefore, mean values for each dog were calculated out of the six values obtained during the diurnal pattern study. On HSI, mean PNa was 145.7 ± 1.0 mmol/l. On LSI, it was significantly lower (142.8 ± 0.4 mmol/l). No significant differences were found among HSI and TBS (146.0 ± 0.4 mmol/l) and TBS (147.6 ± 1.4 mmol/l). In protocol 5 (TBS), PNa decreased significantly after peritoneal dialysis (1300, 141.0 ± 0.9 mmol/l). Afterward it increased again. At 0400 PNa reached 143.6 ± 1.0 mmol/l, a level not statistically different from HSI and LSI values.

**DISCUSSION**

Interactions of renal PDRR are well known. This interplay occurs with mechanisms of Na and volume homeostasis and renal nerve activity (5, 7, 8, 11, 15). Here we study systematically the effects of changes in Na intake and of changes in TBS. In freely moving dogs, diurnal pattern of PRA and stimulus-response curves relating RPP to PRA were obtained.

Diurnal Pattern of PRA: Effects of Na Intake and Changes in TBS

It is generally accepted that PRA is higher during LSI than during HSI. Accordingly, when 24-h mean values of PRA for each dog are compared, those during LSI are higher. However, 24-h mean masks variations within diurnal profile (see Fig. 1). Compared with HSI, PRA on LSI was higher during the first half of the observation period only yet was not significantly different throughout the second half. The diurnal pattern of PRA during HSI resembles that of an earlier study (4). Obviously, the profile is influenced by our standardized experimental regimen. The high PRA measured at 0900 may reflect excitement. Although the actions necessary to conduct the experiments are in general taken without drawing the attention of the dogs in the sound-protected animal room, from 0800 to 0900 calibration of the equipment, cleaning, and feeding was performed. Circulating catecholamines, increased renal nerve activity, and stress are known to increase renin release (5, 7, 15, 17, 20). Interestingly, LSI amplified the renin release related to excitement (0900). This is in accordance with the finding that LSI amplifies the renin response to renal nerve stimulation (18). On the other hand, the physical activity of the dogs was low during the dark period. Accordingly, the PRA differences between HSI and LSI became insignificant (2100, 0100, 0400). However, the effects of Na homeostasis on the diurnal pattern must be taken into account. Intake of Na and water is always achieved between 0830 and 0900. During HSI, this is followed by tremendous increase in Na excretion (4) and by a postprandial suppression (13) of PRA (1300, 1700). During LSI, PRA was not suppressed postprandially in comparison with PRA values obtained from 2100 through 0400. During HSI, Na and water excretion from 2100 through 0800 is low [postabsorptive state (4)]. Thus PRA is higher again during HSI, thereby reaching the PRA level obtained during LSI.

The mechanisms mediating stimulation of renin secretion during LSI, be it plasma volume contraction, lowered PNa, both, or neither (for discussion see Refs. 11, 22, 25), are still under debate. The amplification of renin release related to excitement (0900) may be mediated by low PNa (16, 18). However, PNa was lower...
on LSI than on HSI throughout the observation period, yet PRA was not significantly different during dark and postabsorbent period. Hence it is suggested that the diurnal pattern of PRA during LSI reflects interaction of different mechanisms influencing renin release, and this interaction varies during the day.

From experimental as well as clinical observations it is known that changes in TBS mostly result in inverse changes of PRA. Accordingly, the deficit of TBS induced by peritoneal dialysis increased PRA dramatically, whereas the large surplus of TBS induced in HSI had the opposite effect (Fig. 2). It should be noted that the method used to increase TBS, i.e., 20% reduction of RPP, has a disadvantage: renin release is basically increased (see TBS in Fig. 2). This stimulation exerted by rRPP counteracts suppression of renin release evoked by surplus of TBS. When judging from the diurnal pattern study (in contrast to stimulus-response curves) the effect of surplus of TBS on PRA is underestimated. Nevertheless, the large surplus of TBS induced in HSI effectively suppressed PRA even in the face of > 0.06 mmol Na·kg body wt\(^{-1}\)·day\(^{-1}\). Thus compared with the LSI used (0.5 mmol/kg), one has to reduce Na intake tenfold to achieve a deficit in TBS. However, if TBS is forced below basal level, e.g., by diuretics, there is a state of sodium deficit and an organism’s response to a Na challenge is qualitatively different (26). In accordance with this finding, the relationship of RPP and PRA is not changed by LSI compared with HSI, whereas it is considerably altered by TBS.

Farhi et al. (8) reported that the pressure dependence of PRA is enhanced during LSI. Because furosemide (80 mg/day for 3 days) had been given, it is likely that their dogs were indeed in a state of sodium deficit. However, the differences in methods preclude a comparison to our results during TBS.

As described, PRA was considerably increased during TBS throughout the RPP range studied. Conversely, pressure-dependent PRA was slightly reduced during TBS and considerably suppressed during TBS (see Fig. 4). Thus an inverse relationship between changes in TBS and pressure-dependent PRA was found. To determine the characteristics of this TBS-dependent renin release, as well as its modulation by changes of RPP, Fig. 5 was designed. Here, PRA is plotted as dependent variable against change in TBS (ΔTBS) as an independent variable. Five curves are plotted, each representing the dependence of PRA on TBS at a fixed level of RPP; i.e., within one curve the “isobaric” relationship between renin release and TBS is given. Comparison of the five isobaric curves reveals that the inverse relationship is preserved despite different preset RPP. Therefore, the effects TBS exerts on PRA are not mediated by changes in RPP. However, the lower RPP was set, the steeper the relationship became. Thus TBS-dependent renin release is amplified by PDRR. Moreover, from Fig. 5, another characteristic of TBS-dependent renin release can be derived: when the effect of deficit of TBS (−3.1 mmol Na/kg body wt) is compared with that of a surplus of the same magnitude
(+3.1 mmol), the curves are much steeper during the deficit. Thus the effect that a deficit of TBS exerts on renin release is much greater than that exerted by a surplus.

Mechanisms of TBS-Dependent Renin Release

The pathway by which changes of TBS impinge on renin release is uncertain, although various mechanisms have been supposed (for discussion see Refs. 11, 25, 30). First, concomitant changes in TBW may change plasma volume and, in turn, MABP. Thus PDRR, i.e., the direct impact of RPP on PRA, may mediate the influence of TBS on PRA. However, we found that different TBS resulted in different PRA even at the same RPP; i.e., TBS-dependent renin release is independent from RPP. Furthermore, MABP may influence renin release indirectly. However, this assumption is not supported by our results. Although MABP was not different between ∆TBS and ∆TBS, a striking difference in renin release was found. Likewise, although MABP was not different between LSI and TBS, renin release was. Second, plasma volume changes may impinge on renin release via ANP. Because renin release was different between LSI and TBS despite unchanged ANP, and likewise ANP was not different between ∆TBS and ∆TBS, our results do not favor ANP as a mediator of TBS-dependent renin release. Third, plasma volume changes are detected by atrial receptors, which via neural pathways may influence renin release. Earlier studies (14) have shown, however, that the PRA response to ∆TBS (peritoneal dialysis) in dogs was unchanged after cutting the vagal afferences (cardiac denervation). This does not exclude that this pathway plays a role in mediating suppression of renin release during surplus of TBS.

Furthermore, distal tubular NaCl load and renal arterial PNa are known to influence renin release (11, 22), whereby Na movements across the membrane of juxtaglomerular cells are suggested to play a crucial role (23). Based on our results during ∆TBS, we hypothesize that such Na shifts may contribute in mediating TBS-dependent renin release. By means of peritoneal dialysis, Na but not water was withdrawn. Consequently, PNa decreased after dialysis. Afterward, PNa increased again. As has been shown earlier (1), this increase in PNa is partly achieved by a shift of Na from intracellular to extracellular space. This Na shift may have contributed to increased PRA. However, further investigations are needed to determine the role of intracellular-extracellular Na shifts in mediating TBS-dependence of renin release.

In conclusion, this study reveals that basal as well as pressure-dependent PRA is modified by changes of TBS rather than by different amounts of Na intake. In particular, LSI did not enhance the pressure dependence of PRA compared with HSI. However, a deficit of TBS increased basal as well as pressure-dependent PRA, whereas a large surplus of TBS suppressed it. Thus an inverse relationship between TBS and PRA was found. The pathways, which may mediate this TBS-dependent renin release, remain obscure. We found that the TBS-dependence of PRA is preserved despite different preset RPP. Thus TBS-dependent renin release is not mediated by changes in RPP. In addition, our results indicate that changes of ANP and systemic arterial pressure do not play a significant role in mediating TBS-dependent renin release.

Perspectives

Two characteristics of TBS-dependent renin release may have particular physiological relevance. First, the steepness of the relationship between PRA and TBS, i.e., the TBS-dependence of PRA, is enhanced by decreasing RPP. This interaction between TBS-dependent renin release and PDRR enables the organism, via the RAAS, to react in a differentiated manner to challenges of Na homeostasis and circulatory control. Second, the effect that a deficit of TBS exerts on renin

Fig. 5. Scheme depicting dependence of PRA on changes in total-body sodium (∆TBS). Each of 5 curves represents relationship of PRA and ∆TBS for a fixed level of RPP ("isobaric" relationship, RPP given at left). For details see DISCUSSION. Mean values of PRA at respective RPP (as given in Fig. 4) were related to mean values of ∆TBS of protocols |TBS, |TBS, and |TBS. Data at ∆TBS = 0 represent mean values of 16 dogs on HSI and LSI (TBS difference between HSI and LSI = 0.3 mmol/kg; for details see RESULTS).
release is much greater than that exerted by a surplus. From a teleological point of view this appears reasonable: an organism adapted to live on land is forced to cope with a deficit rather than to excrete a surplus of Na and water.

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