

Chloride-Dominant Salt Sensitivity in the Stroke-Prone Spontaneously Hypertensive Rat

Olga Schmidlin, Masae Tanaka, Andrew W. Bollen, Sai-Li Yi, R. Curtis Morris, Jr

Abstract—We tested the hypothesis that in the stroke-prone spontaneously hypertensive rat (SHRSP), the Cl^- component of dietary NaCl dominantly determines its pressor effect (salt-sensitivity). We telemetrically measured systolic aortic blood pressure (SBP) in SHRSP loaded with: nothing (CTL); NaCl alone (NaCl) (44 mmol/100 grams chow); KCl (KCl) alone (44 mmol); NaCl (44 mmol) combined with KHCO_3 (77 mmol) (NaCl/KBC) or with KCl (77 mmol) (NaCl/KCl). Across all groups, from age 10 to 15 or 16 weeks, SBP increased linearly (mm Hg/week) (dp/dt, change in SBP as a function of time): CTL, 5.6; NaCl, 9.5; KCl, 8.8; NaCl/KBC, 9.1; and NaCl/KCl, 14.6. Thus, the value of dp/dt in KCl matched that in NaCl. The value of dp/dt in NaCl/KCl exceeded that in NaCl in direct proportion to the greater Cl^- load. Across all groups, only Cl^- load bore a direct, highly linear relationship with dp/dt. Strokes occurred only, but always with SBP >250 mm Hg, a value observed almost exclusively in NaCl/KCl. Thus, Cl^- dominantly determined the pressor effect induced with dietary NaCl, both with NaCl loaded alone and combined with either KCl or KHCO_3 , and thereby likely determined the occurrence of stroke with NaCl loading. Over the initial 3-day period of NaCl loading and exacerbating hypertension, external balance of Na^+ increased similarly among all groups. However, within 24 hours of initiating NaCl loading, urinary creatinine excretion decreased in direct proportion to dp/dt and urinary Cl^- excretion. We conclude that in the SHRSP, the Cl^- component of a dietary NaCl dominantly determines salt sensitivity and thereby phenotypic expression. We suggest that Cl^- might do so by inducing renal vasoconstriction. (*Hypertension*. 2005; 45:867-873.)

Key Words: chlorides ■ potassium ■ rats, stroke-prone spontaneously hypertensive ■ sodium

It is widely formulated or tacitly assumed that all pressor “sensitivity” to dietary NaCl depends on both its Na^+ and Cl^- components, and on each ion to a similar extent.^{1–5} In fact, in humans and animals with salt-sensitive hypertension, selective dietary loading of Na^+ and of Cl^- has repeatedly failed to induce a pressor effect.^{3,6–14} Yet, in the spontaneously hypertensive rat (SHR),¹⁵ selective Cl^- loading with glycine and choline chloride combined induced an exacerbation of hypertension but also an apparent systemic toxicity that complicated its interpretation.¹⁶ In the more salt-sensitive genetic substrain of the SHR, the stroke-prone SHR (SHRSP),¹⁷ selective Cl^- loading with KCl exacerbated hypertension and microangiopathic nephropathy and induced numerous strokes,^{18,19} much as does NaCl loading,²⁰ but not NaHCO_3 loading.¹² Thus, in the SHRSP, the Cl^- component of dietary NaCl might dominantly determine the expression of salt sensitivity. If so, Cl^- load might determine the severity of hypertension with NaCl loading, both when loaded alone and when combined with either KCl or KHCO_3 loading. We report these positive tests of the hypothesis.

Methods

Male SHRSP (University of Iowa, Iowa City, Iowa) were fed a Japanese-style diet (0.5% K^+ and 0.4% NaCl; Zeigler Bros, Inc, Gardners, Pa) from 6 weeks of age until they were euthanized at 15 weeks. Until randomization, but not afterward, this diet was supplemented in all rats with 1.5% K^+ supplied as KHCO_3 . At 10 weeks, the NaCl content of the diet was increased to 2.6% and rats were randomly assigned to 3 groups: (1) NaCl alone, no K^+ supplement (NaCl; n=15); (2) NaCl plus 2.5% K^+ as KCl (NaCl/KCl; n=15); or (3) NaCl plus 2.5% K^+ as KHCO_3 (NaCl/KBC; n=16). De-ionized drinking water was supplied ad libitum. All groups were fed and housed as before¹⁸ and studied according to the guidelines of the University of California, San Francisco, Committee on Animal Research.

In each rat at 8 weeks of age, we implanted intraperitoneally a radiotelemetric blood pressure-measuring device with a pressure-sensing catheter inserted into the infrarenal aorta (model TA11PA; Data Sciences International, St. Paul, Minn).¹⁸ In each rat, we calculated successive mean weekly values of systolic blood pressure (SBP) and diastolic blood pressure from measurements obtained over 5-second intervals every 10 minutes. “Final” SBP is the average SBP calculated from the last 3 days before euthanization or death. For analysis of “initial pressor effects,” ie, pressure changes occurring within the first 3 days after assignment, we calculated 24-hour daily mean values of SBP as well as 12-hour day and night values.

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TABLE 1. Blood Pressure, Urine Electrolytes, and Body Weight

Variable	NaCl/KCl	NaCl	KCl	NaCl/KBC	CTL	P ANOVA	Newman-Keuls Test§
n	15	15	17	16	20	NA	
SBP, mm Hg*							
Baseline	175 (170/180)	174 (170/179)	176 (170/181)	173 (170/176)	179 (174/185)	NS	
Week 4	235 (222/247)	211 (201/220)	210 (203/218)	209 (198/220)	201 (194/208)	0.0001	NaCl/KCl > (NaCl=KCl=NaCl/KBC=CTL)
Change	60 (50/70)	37 (30/44)	35 (29/40)	36 (27/36)	21 (17/25)	0.000000000	NaCl/KCl >all others; CTL <all others; NaCl=KCl=NaCl/KBC
Urinary electrolyte excretion (week 4), mmol/d per 100 grams BW†							
Na ⁺	3.2 (3.0/3.4)	3.2 (2.9/3.5)	0.5 (0.4/0.6)	3.2 (2.8/3.3)	0.4 (0.3/0.5)	NA	
Cl ⁻	6.6 (6.0/7.2)	3.3 (3.1/3.5)	3.1 (2.9/3.2)	2.6 (2.3/2.8)	0.6 (0.5/0.6)	NA	
K ⁺	5.2 (4.7/5.5)	1.1 (1.0/1.2)	3.8 (2.6/4.3)	5.2 (4.9/5.5)	1.5 (1.2/1.7)	NA	
Na ⁺ /K ⁺ ratio	0.63 (0.59/0.67)	2.8 (2.5/3.0)	0.13 (0.11/0.13)	0.58 (0.55/0.61)	0.31 (0.23/0.43)	NA	
BW, grams *							
Baseline	223 (214/230)	225 (219/231)	218 (209/230)	218 (210/226)	218 (209/227)	NS	
Week 4 ‡	262 (244/281)	269 (263/276)	273 (264/282)	254 (243/266)	274 (264/284)	NS	

*Mean (95% CI).

†Median (25th/75th percentile).

‡Means adjusted for the occurrence of strokes.

§P<0.05 is considered significant.

BW indicates body weight; CTL, controls; NA, not available; NS, not significant; SBP, systolic blood pressure.

We examined rats daily for signs of stroke such as irritability, lethargy, akinesia, and convulsions.²¹ On the death of each rat, one of the investigators (A.W.B.) examined its brain for pathological abnormalities without knowledge of the experimental group, blood pressure, or signs of stroke. Stroke was judged to have occurred only in rats with pathological evidence of stroke, all but 1 of which had clinical signs of stroke.

Body weight (BW) of each rat was measured weekly. The 24-hour urinary excretion rates of Na⁺ (UVNa), K⁺ (UVK), Cl⁻ (UVCl), creatinine (UVcr), and total protein (UVP) were measured at baseline (age 9 weeks) and on days 1, 2, 3, 10, 17, and 31 after assignment. Na⁺ and Cl⁻ balances, calculated as the difference of urinary output and dietary intake, were assessed over two 3-day periods before and immediately after NaCl loading, respectively. Surviving rats were euthanized at age 15 weeks and tracheal blood samples were obtained to measure plasma renin activity (PRA) by radioimmunoassay (RIA).²²

To compare the pressor effect of dietary NaCl loading (2.6%) to that of an equimolar amount of Cl⁻ loading without Na⁺ (as KCl) and to that without Cl⁻ loading (dietary NaCl 0.4%), blood pressure data of 2 additional groups of SHRSP (KCl) (n=17) and controls (CTL) (n=20) are included in the current analysis.¹⁸ The physical provenance, experimental conditions, and techniques used to measure blood pressure were the same as described except that 7-day mean SBP values were collected at 2-week intervals over a 6-week period.

For statistical analysis, we used the Statistica software package (Statsoft Inc). Because the values of SBP over time described a linear trajectory in all groups, we used a least-squares estimation to assess in individual rats the time course of SBP increase (dp/dt) of both the 24-hour daily mean SBP from 0 to 3 days (initial pressor effects) and the 24-hour weekly mean SBP from 0 to 5 or 6 weeks (long-term pressor effects). We assessed group differences in dp/dt, Na⁺ balance, and change in UVcr with ANOVA followed by the Newman-Keuls test, and differences in UVCl, UVP, and PRA with the Kruskal-Wallis test, followed by the Mann-Whitney test. For within-group comparisons of outcomes not normally distributed, we used the Wilcoxon signed rank test. To compare the frequency of strokes among groups, we used the χ^2 test. To assess interrelationships between variables, we used simple linear and forward stepwise multiple regression analyses. Data are presented as mean and 95% confidence interval (CI) or median and 25th/75th percentile. P<0.05 was considered statistically significant.

Results

Baseline Blood Pressure

In 9- to 10-week-old rats, before assignment, BP was similar in all groups (Table 1). Blood pressure values showed circadian variation with average baseline day SBP being \approx 11 mm Hg lower than average night SBP. Throughout the study, values of SBP and diastolic blood pressure in individual rats varied with each other directly and highly significantly ($R^2=0.964$, $P<0.0001$). Therefore, SBP values only were used for analyses.

Pressor Effects of Loading Either NaCl or KCl Alone, or NaCl Combined With Either KCl or KHCO₃, or No Salt (Control)

After assignment, SBP increased in a highly linear fashion in all 5 groups throughout the 5 or 6 weeks of observation. The average values of dp/dt (mm Hg/week; mean and 95% CI) were: NaCl/KCl, 14.6 (12.1/17.0); NaCl, 9.5 (7.6/11.4); KCl, 8.8 (7.2/10.3); NaCl/KBC, 9.1 (6.7/11.5); and CTL, 5.6 (4.6/6.6; ANOVA $P<0.0001$; Figure 1A). In NaCl/KCl, the value of dp/dt was significantly greater than that occurring in any of the 4 other groups ($P<0.001$ for each comparison). In CTL, the value of dp/dt was significantly less than that occurring in any of the 4 other groups ($P<0.05$ for each comparison). In NaCl, KCl, and NaCl/KBC, all of which receiving the same amount of dietary Cl⁻ (Figure 1A), the values of dp/dt were not different from each other. Four weeks after assignment, SBP had increased significantly more in NaCl/KCl than in any of the 4 other groups (ANOVA $P<0.0001$; Table 1). The average value of dp/dt of each group was directly and linearly related to both the average UVCl ($R^2=0.995$, $P<0.0002$; Figure 1B) and the dietary level of Cl⁻ ($R^2=0.992$, $P<0.0003$) but not to UVNa ($P=0.2$) or the dietary level of Na⁺ ($P=0.2$), the urinary Na⁺/K⁺ ratio ($P=0.8$), or the dietary Na⁺/K⁺ ratio ($P=0.7$).

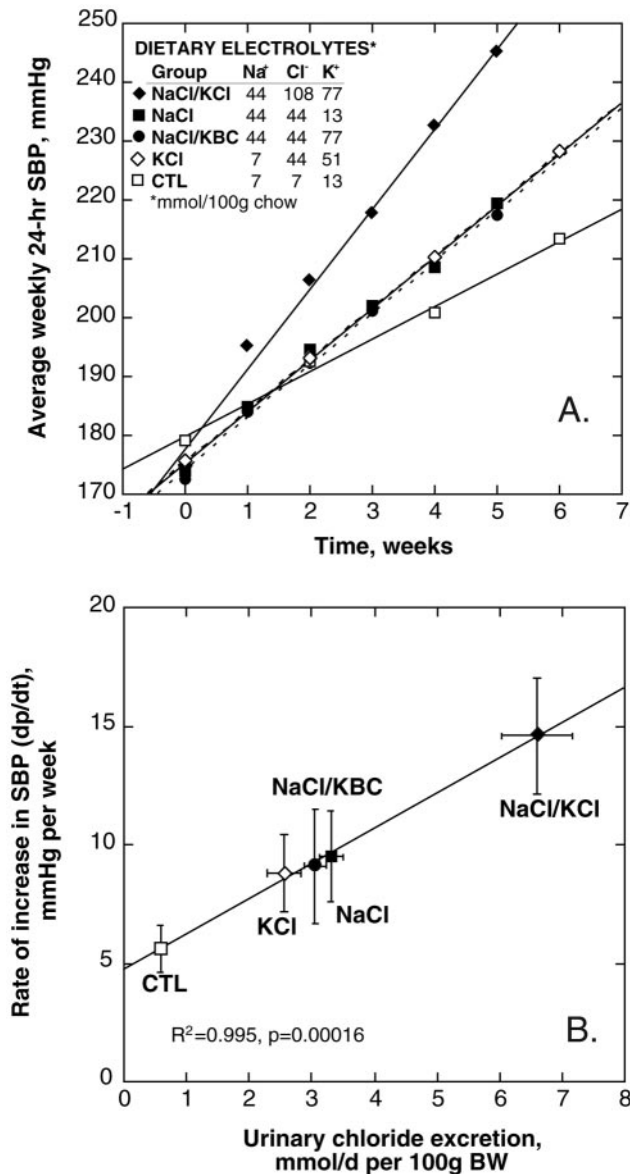


Figure 1. A, Time course of SBP in SHRSP fed various amounts of Cl^- , Na^+ , and K^+ over a period of 5 or 6 weeks. NaCl/KCl (◆), NaCl (■), NaCl/KBC (●), KCl (◇), and control (CTL) (□). In all groups, SBP increased linearly with time. NaCl loading alone and KCl loading alone induced similar exacerbations of hypertension. Combining NaCl loading with KCl loading, which imposed a Cl^- load more than twice that of NaCl loading alone, induced an exacerbation of hypertension more than twice that of NaCl loading alone. B, Relationship between urinary Cl^- excretion and the rate of increase in SBP. The average rate of increase in SBP (dp/dt) in each group is directly and linearly related to the average urinary Cl^- excretion ($R^2=0.995$, $P=0.00016$) but not to the urinary Na^+/K^+ ratio ($R^2=0.0169$, $P=0.835$), not shown.

Initial Pressor Effect in NaCl-Loaded Rats

Throughout the 3-day period immediately before assignment, SBP did not change. In NaCl/KCl, the increase in 24-hour SBP (mm Hg, mean, and 95% CI) on the first day after assignment was 9 (6/12), at least twice that in either NaCl, 1 (−1/3), or NaCl/KBC, 4 (2/5) (ANOVA $P<0.00002$; NaCl/KCl > NaCl/KBC=NaCl; Figure 2A). As judged by the significant increase in the day–night difference of SBP, the

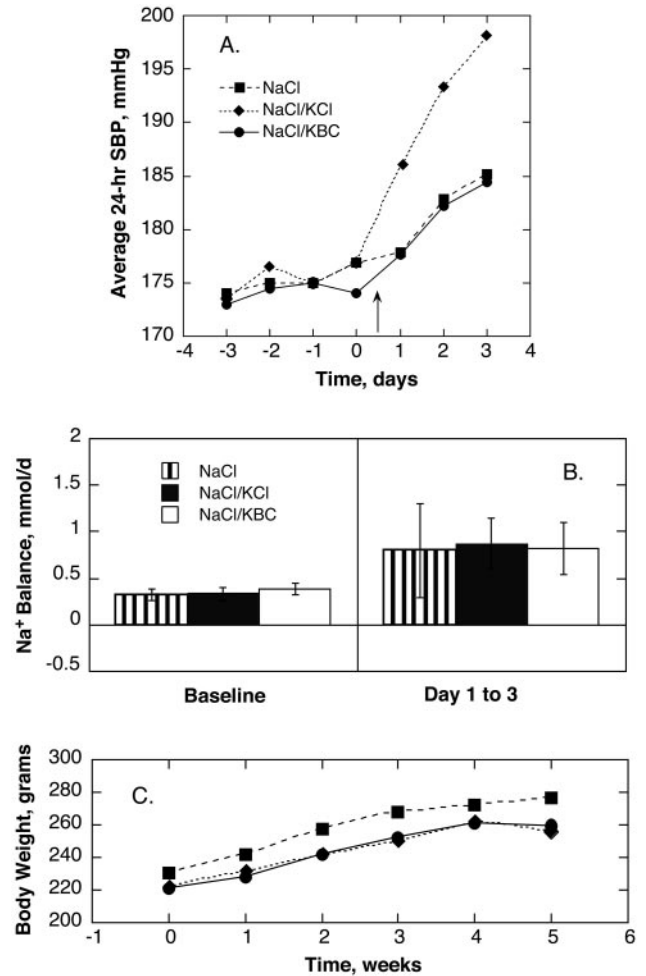


Figure 2. A, Time course of 24-hour SBP immediately before and after initiation of NaCl loading alone (NaCl) or in combination with either KCl loading (NaCl/KCl) or KHCO_3 loading (NaCl/KBC). The arrow denotes the time at which electrolyte loading was initiated. NaCl loading combined with KCl loading, but not NaCl-loading alone, induced a significant increase in SBP within 24 hours. B, Average sodium balance during the two 3-day periods immediately before and after initiation of NaCl loading alone or in combination with either KCl loading or KHCO_3 loading. When dietary NaCl was increased from 0.4% to 2.6%, sodium retention increased in all groups and to a similar extent. C, Median BW. BW increased progressively and similarly with age in all groups of NaCl-loaded rats.

pressor effect of NaCl combined with KCl was apparent within 12 hours of assignment, ie, after the first electrolyte loading. The average rate of increase in 24-hour SBP during the 3-day period immediately after assignment (initial dp/dt, mm Hg/d; mean and 95% CI) was: NaCl/KCl, 7.2 (6.4/7.9); NaCl alone, 3.0 (2.2/3.8); and NaCl/KBC, 3.6 (2.8/4.3) (NaCl/KCl versus NaCl and versus NaCl/KBC, $P<0.0002$). The initial dp/dt was a significant predictor for the increase in 24-hour SBP 5 weeks after assignment ($R^2=0.341$, $P<0.0001$).

Electrolyte Excretion and BW in NaCl-Loaded Rats

Baseline UVNa and UVCl and Na^+ and Cl^- balances were similar among groups. After initiating dietary NaCl load,

TABLE 2. Effects of NaCl/KCl, NaCl, and NaCl/KBC on Renal Function

Variable	NaCl/KCl	NaCl	NaCl/KBC	P	Post hoc Test
Urine creatinine excretion, mg/d*					
Baseline	10.8 (10.3/11.2)	10.6 (10.4/11.0)	10.2 (9.7/10.6)	NS‡	NS‡
Day 1 to 3 average	6.9 (6.6/7.2)	8.0 (7.6/8.5)	8.9 (8.4/9.4)	0.00000‡	NaCl/KBC>NaCl>NaCl/KCl
Change from baseline, mg/d	-3.9 (-4.4/-3.4)	-2.6 (-3.1/-2.1)	-1.3 (-1.8/-0.8)	0.00000‡	NaCl/KCl>NaCl>NaCl/KBC
Change from baseline, %	-7 (-39/-32)	-24 (-28/-19)	-12 (-17/-8)		
Day 31	8.2 (7.6/8.8)	10.1 (9.7/10.5)	12.0 (11.2/12.8)	0.00000‡	NaCl/KBC>NaCl>NaCl/KCl
Urine protein excretion, mg/d†					
Baseline	48 (41/57)	50 (43/55)	46 (39/50)	NS§	
Day 1 to 3 average	34 (31/47)	43 (41/48)	33 (27/40)	0.04§	NaCl>NaCl/KBC
Change from baseline, mg/d	-11 (-15/-5)	-3 (-21/3)	-11 (-20/-5)	NS§	
Change from baseline, %	-26 (-51/-11)	-3 (-43/3)	-24 (-60/-12)		
Day 31	497 (55/551)	94 (55/286)	128 (45/323)	0.006§	NaCl/KCl>(NaCl=NaCl/KBC)
PRA, ng/mL per h†¶	34 (14/57)	23 (6/35)	13 (5/67)	NS§	

*Mean (95% CI).

†Median (25th/75th percentile).

‡ANOVA followed by Newman-Keuls test.

§Kruskal-Wallis followed by Mann-Whitney U test.

¶PRA values were obtained at time of euthanization.

||P<0.05 is considered significant.

PRA indicates plasma renin activity.

average Na^+ balance was slightly more positive than before but did not differ between groups (Figure 2B). UVCl increased significantly in all groups from an average baseline value of 0.78 (0.76/0.80) mmol/d per 100 grams BW to 3.7 (3.5/3.9) in NaCl, 8.2 (7.9/8.6) in NaCl/KCl, and 2.9 (2.7/3.1) in NaCl/KBC. Consistent with the greater Cl^- load, UVCl remained $\approx 2.5\times$ greater in NaCl/KCl than in NaCl and in NaCl/KBC throughout the study (Table 1). Average 3-day Cl^- balance was significantly more positive in NaCl/KCl (3.4 ± 0.8 mmol/d) than in either NaCl (0.4 ± 0.4 mmol/d) or NaCl/KBC (0.8 ± 0.3 mmol/d).

BW was not different among groups at baseline. BW increased progressively and similarly with age in all groups (Figure 2C and Table 1). However, in rats with signs of stroke, it increased less than in those with no signs.

Renal Function in NaCl-Loaded Rats

Baseline UVcr did not differ among groups (Table 2). Within 24 hours of assignment, UVcr decreased significantly in all groups (ANOVA $P<0.0001$). However, the decrease in NaCl/KCl was at least twice that in either NaCl or in NaCl/KBC (Figure 3A). Across all 3 groups, the extent to which UVcr decreased during the first 3 days varied directly and significantly with baseline SBP (β -coefficient -0.344 , $P=0.005$) and the initial dp/dt (β -coefficient -0.586 , $P<0.0001$; Figure 3B) (overall $R^2=0.426$, $P<0.0001$). On the first day of NaCl-loading, the decrease in UVcr varied directly and significantly with UVCl ($R^2=0.471$, $P<0.0000$; Figure 3C) but not with UVNa.

Baseline UVP did not differ among groups. UVP did not increase during the first 3 days after assignment (Table 2), when UVcr decreased by as much as 40% in some animals. In none of the groups was the value of UVP significantly greater than that at baseline 17 days after assignment, whereas 31

days after assignment the value was significantly greater in all groups. In NaCl/KCl UVP was ≈ 5 -times that in either NaCl or NaCl/KBC ($P<0.01$; Table 2).

PRA values did not differ among groups (Table 2) but log-transformed PRA values varied directly with final SBP ($R^2=0.663$, $P<0.0001$).

Occurrence of Strokes in NaCl-Loaded Rats

Strokes occurred in 8 NaCl/KCl, in 0 NaCl, and in 2 NaCl/KBC ($P<0.002$). Strokes were significantly more frequent in NaCl/KCl than in either NaCl ($P<0.01$) or NaCl/KBC ($P<0.05$). Stroke frequency did not differ between NaCl and NaCl/KBC.

Discussion

In the SHRSP that is not NaCl-loaded, we recently reported that whereas supplementing dietary K^+ with either K-citrate or KHCO_3 attenuates hypertension, supplementing dietary K^+ with KCl exacerbates it.¹⁸ That such a pressor effect of the Cl^- component of KCl overrides an otherwise antipressor effect of supplemental K^+ indicates the strength of the pressor effect of dietary Cl^- in the SHRSP. That supplementing dietary Cl^- induces its pressor effect without supplementing dietary Na^+ indicates that in the SHRSP dietary Cl^- is selectively sufficient to induce a pressor effect. That the Na^+ component of dietary NaCl is not selectively sufficient to induce a pressor effect in the SHRSP is indicated by the observation in this rat that NaHCO_3 loading did not exacerbate hypertension.¹² That NaCl-loading does exacerbate hypertension in the SHRSP¹² accords then with the hypothesis that in this rat the Cl^- component of dietary NaCl dominantly determines the expression of salt sensitivity.¹⁸ This hypothesis can be tested with considerable rigor by selectively loading Cl^- with KCl, given the antipressor effect of K^+

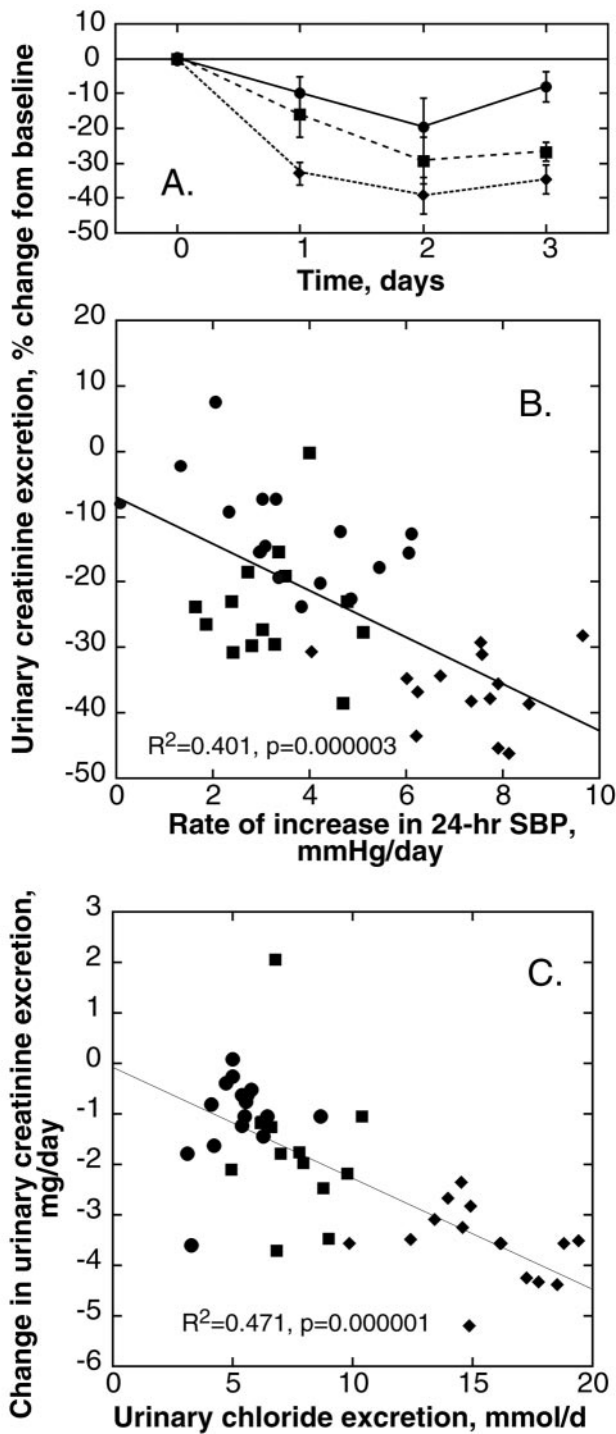


Figure 3. A, Time course of urinary creatinine excretion (UVcr) during the initial 3 days of NaCl loading alone (NaCl) or in combination with either KCl loading (NaCl/KCl) or KHCO_3 loading (NaCl/KBC). Data are depicted as percent change from baseline. Baseline UVcr did not differ among groups. Within 24 hours of initiating NaCl loading, UVcr decreased in all groups but twice as much with NaCl/KCl (\blacklozenge) as with either NaCl (\blacksquare) or with NaCl/KBC (\bullet). B, Relationship between the percent change in UVcr and the rate of increase in 24-hour SBP observed over the initial 72-hour period of NaCl loading alone or in combination with either KCl loading or KHCO_3 loading. C, Relationship between urinary Cl^- excretion and the decrease in UVcr during the initial 24-hour period of NaCl loading alone or in combination with either KCl loading or KHCO_3 loading.

loaded without Cl^- in the SHRSP.¹⁸ Thus, a positive test of the hypothesized Cl^- -dominant salt sensitivity is provided by the current observation in the SHRSP that equimolar amounts of NaCl and KCl loaded separately induced similar pressor effects.

If Cl^- does dominantly determine the pressor effect of dietary NaCl in the SHRSP, that effect in this rat might be amplified by KCl loading. In fact, we find in the SHRSP that the pressor effect of NaCl loaded in combination with KCl is more than twice that of NaCl loaded alone, and directly proportionate to the more-than-twice greater Cl^- load imposed by KCl. By contrast, the pressor effect of NaCl loaded in combination with KHCO_3 is indistinguishable from that of NaCl loaded alone. The dp/dt bore a direct relationship to the Cl^- load, and to it alone, across all loads of Cl^- , Na^+ , and K^+ . The current observations provide the first demonstration in a state of salt-sensitive hypertension that dietary Cl^- can dominantly and dose-dependently determine the severity of hypertension, both when dietary NaCl is loaded alone and when combined with either dietary KCl or KHCO_3 . In so establishing the fact of Cl^- -dominant salt sensitivity, this demonstration documents that the pressor effect of dietary NaCl can involve more than symmetric effects of its component ions.

In sharp contrast to the current observations, it has been repeatedly observed that KCl-loading attenuates salt-sensitive hypertension in its archetypal genetic model, the Dahl S rat,^{7,23} and in its archetypal acquired model, that induced by desoxycorticosterone.^{24,25} K^+ loading induces natriuresis by directly reducing renal tubular reclamation of Na^+ .^{26,27} Thus, an attenuating effect of KCl-loading on salt-sensitive hypertension accords with the pathophysiological mechanism generally formulated to initiate the syndrome^{1,2,4,5}: Excessive renal tubular reclamation of dietary NaCl entrains similarly positive external balances of both Na^+ and Cl^- that jointly effect plasma volume expansion by directly increasing extracellular osmotic activity. Although Na^+ and Cl^- are the dominant dietary determinants of extracellular osmotic activity, that activity is much less affected by dietary K^+ , the distribution of dietary K^+ retained being predominantly not extracellular. Thus, in the current study of the SHRSP, an increase in extracellular osmotic activity is not a pathophysiological event that likely explains how NaCl and KCl induced similar pressor effects when loaded separately in equimolar amounts and summative pressor effects when loaded in combination (and in a distribution heavily weighted toward KCl). Further, although NaCl and KCl loaded in combination induced a pressor effect twice that induced by NaCl loaded alone, the greater effect occurred without greater increases either in positive Na^+ balance or in body weight. We conclude that the pathophysiological mechanism mediating salt-sensitive hypertension in the SHRSP is distinct from that generally formulated. Specifically, in the SHRSP, the Cl^- component of dietary NaCl has its own major pressor agency, one apart from any conferred only by the mutually complementary extracellular osmotic activities of Na^+ and Cl^- and their joint effecting of plasma volume expansion.

Given the primacy of altered renal function in the pathogenesis of hypertension in the SHRSP,²⁸ in this rat the Cl^-

component of NaCl could have a major pressor agency by inducing or amplifying an alteration of renal function. That Cl^- per se might do so clearly runs counter to the general view that the Cl^- component of NaCl, like its Na^+ component, is only an object, not an agent, of altered renal function that mediates salt-sensitive hypertension.^{1,2,4,5} However, in the current study, urinary creatinine excretion decreased by one-third within 24 hours of initiating the combined loading of NaCl and KCl, and within 12 hours, hypertension was exacerbated. When NaCl loaded alone induced a lesser exacerbation of hypertension, urinary creatinine excretion also decreased sharply within 24 hours, but by only half as much. Urinary protein excretion remained unincreased 2 weeks after initiating Cl^- loading, suggesting that Cl^- loading induced an immediate dose-dependent reduction in glomerular filtration rate without inducing renal damage. The magnitude of the immediate decrease in creatinine excretion varied directly with the magnitude of both the immediate and ultimate increase in BP induced by Cl^- loading, and with the urinary excretion of Cl^- , but not of Na^+ .

In the SHR, and presumably also in the SHRSP, hypertension is likely caused by a genetically determined narrowing of the renal afferent arteriole^{29–31} that is susceptible to physiological³² and pharmacological modulation.^{33,34} In the SHR, pharmacological inhibition of the angiotensin converting enzyme dose-dependently attenuates hypertension and the narrowing of the renal afferent arteriole,^{33,34} the extent of narrowing varying directly with the severity of pharmacologically attenuated hypertension.³³ Even in the normal rat, Cl^- selectively loaded either in the diet^{13,14} or in the isolated perfused kidney³⁵ induces renal vasoconstriction and amplifies that induced by angiotensin II,^{14,36} likely by constricting the renal afferent arteriole³⁷ such that glomerular filtration rate is reduced.³⁵ An increased delivery of Cl^- to the macula densa of the thick ascending limb of the renal tubule, as presumably occurred with the chlorureses currently induced in the SHRSP, elicits dose-dependent constriction of the renal afferent arteriole as part of the normal tubuloglomerular feedback (TGF) response.³⁸ In the SHR, an angiotensin II-dependent exaggeration of TGF is a likely major determinant of the severity of hypertension.^{39–41} A similar determinacy is likely in the SHRSP, in which the renal vasoconstrictive response to angiotensin II is also exaggerated.⁴² Thus, in the SHRSP, the Cl^- component of dietary NaCl might dominantly determine the expression of salt sensitivity by determining the extent to which the renal afferent arteriole is further narrowed.

In the current study of the NaCl-loaded SHRSP, and in a previous study of the SHRSP fed a low-normal Na^+ diet,¹⁸ numerous strokes occurred only, but invariably when KCl loading exacerbated hypertension to levels of blood pressure of ≥ 250 mm Hg. In the NaCl-loaded SHRSP, this effect of KCl differs from that in which KCl loading reduced the frequency of stroke, and without affecting the measured severity of hypertension.⁴³ “Genetic drift” in disease expression might explain the difference.⁴⁴

Perspectives

The fact of Cl^- -dominant salt sensitivity raises the possibility that in some humans, the initiating pathophysiology of salt

sensitivity might involve a genetically determined enhancement of not only the renal tubular reclamation of NaCl but also the renal vasoconstrictive effect of its Cl^- component. Accordingly, genetically enhanced, chloride-mediated renal vasoconstriction might so physiologically amplify genetically enhanced renal tubular reclamation of NaCl as to render pressor genetic defects and dietary loads of NaCl that otherwise are not.

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