Neuronal Responsiveness to Central Na⁺ in 2 Congenic Strains of Dahl Salt-Sensitive Rats

Bing S. Huang, Monir Ahmad, Alan Y. Deng, Frans H.H. Leenen

Abstract—Dahl salt-sensitive rats show increased Na⁺ entry into the brain on high salt intake and increased sympathetic and pressor responses to central Na⁺. We examined C10QTL2 and C17QTL to test whether they contribute to these phenotypes. In Dahl salt-sensitive, Lewis, and C10S.L16, and C17S.L2 congenic rats on a high salt diet for 8 to 10 days, blood pressure and heart rate were higher in Dahl salt-sensitive versus others and in C10S.L16 and C17S.L2 versus Lewis rats. Cerebrospinal fluid [Na⁺] increased by ∼5 mmol/L in Dahl salt-sensitive, C10S.L16, and C17S.L2 compared with Lewis rats. In rats on a regular salt diet, 8-minute intracerebroventricular infusions of artificial cerebrospinal fluid with increasing [Na⁺] caused increases in blood pressure, heart rate, and renal sympathetic nerve activity, which were ≈90% larger in Dahl salt-sensitive and C17S.L2 versus Lewis rats and only 35% to 45% larger in C10S.L16 versus Lewis rats. In another set of rats on regular salt, blood pressure and heart rate were recorded by telemetry before and during intracerebroventricular infusion of Na⁺-rich cerebrospinal fluid for 14 days. Na⁺-rich cerebrospinal fluid caused significantly larger increases in blood pressure and heart rate, larger responses to air stress and more impairment of baroreflex in Dahl salt-sensitive and C17S.L2 rats versus Lewis rats. In contrast, responses in C10S.L16 rats were similar to those in Lewis rats. These data suggest that, in Dahl salt-sensitive rats, genetic variants in C10QTL2 but not C17QTL contribute to increased neuronal responsiveness to cerebrospinal fluid [Na⁺] induced by high salt. (Hypertension. 2007; 49:1315-1320.)

Key Words: brain ■ sodium ■ sympathetic activity ■ blood pressure ■ telemetry ■ congenic strains of Dahl rats

Central nervous system (CNS) mechanisms play an essential role in the development of salt-induced hypertension in Dahl salt-sensitive (S) rats. On high salt intake, [Na⁺] in the cerebrospinal fluid (CSF) increases in Dahl S but not salt-resistant (R) rats, which may occur either 1 day before or after the BP increases. In addition, sympathoexcitatory and pressor responses to an increase in CSF [Na⁺] by central infusion of Na⁺-rich CSF are markedly enhanced in Dahl S compared with Dahl R and Wistar rats. Sympathetic hyperactivity and hypertension in Dahl S rats on high salt and by central infusion of Na⁺-rich CSF can be prevented by CNS blockade of mineralocorticoid receptors, epithelial Na⁺ channels (ENaCs), "ouabain," or angiotensin type 1 receptors. The increases in CSF [Na⁺] in Dahl S rats on high salt intake are prevented by CNS blockade of ENaCs with benzamil. We hypothesized that genetic variants in genes regulating activity of CNS pathways involving mineralocorticoid receptors, ENaC, "ouabain," and angiotensin type 1 receptors contribute to increased Na⁺ entry into the CSF and brain and enhanced sympathetic and pressor responses to brain Na⁺.

Studies on genetic factors of hypertension established multiple quantitative trait loci (QTLs) for blood pressure (BP) on different chromosomes. For example, on chromosome 10, 4 BP QTLs were defined, namely C10QTL1, C10QTL2, C10QTL3, and C10QTL4. One BP QTL, C17QTL, was also defined on chromosome 17 of Dahl S rats. For a recent list of QTLs localized in the Dahl rats, see Table 1 in Reference 12. The identification of "intermediate phenotypes" is an essential step to elucidate the actual physiological mechanisms through which QTLs contribute to BP regulation. So far, no functional studies have been performed in Dahl S rats that associate any of these QTLs to neuronal mechanisms, such as increases in CSF [Na⁺] (CSF [Na⁺]↑) on high salt intake and enhanced sympathoexcitatory and pressor responses to CSF [Na⁺]↑. We initiated detailed physiological studies of C10QTL2 and C17QTL to detect possible intermediate phenotypes to which their BP effects could be connected. These 2 QTLs were chosen at random to represent QTLs on 2 different chromosomes as a foundation for physiological analyses of other QTLs. The C10QTL2 interval spans 4.6 Mb and includes ≈65 genes. The C17QTL interval carries 35 Mb and contains ≈316 genes.

In the present study, we evaluated in the congenic strains, C10S.L16 (ie, the carrier of C10QTL2) and C17S.L2 (ie, the...
carrier of C17QTL), and their parental strains Dahl S and Lewis rats: (1) effects of high salt intake for 8 to 10 days on CSF [Na\(^+\)] and resting BP and heart rate (HR); (2) increases in BP, HR, and renal sympathetic nerve activity (RSNA) in response to brief intracerebroventricular (icv) infusions of CSF at increasing concentrations of Na\(^+\); and (3) effects of icv infusion of Na\(^+\)-rich CSF for 14 days on 24-hour BP and HR, as well as BP and HR responses to air stress and baroreflex control of HR. The latter 2 studies were performed in rats on regular salt intake.

**Methods**

C10S.L16 and C17S.L2 congenic rats were constructed, and their chromosome coverage was described previously.\(^{13,14}\) Female pregnant Dahl S, Lewis, C10S.L16, and C17S.L2 congenic rats were shipped from Montreal and bred at the animal facilities of the University of Ottawa Heart Institute. The rats were housed on a 12-hour light/dark cycle and fed a standard commercial rat chow (101 μmol of Na\(^+/\)g; Harlan Sprague Dawley Inc) and water ad libitum. The studies were carried out in accordance with the guidelines of the Canadian Council on Animal Care, which conform to National Institutes of Health guidelines for the care and use of laboratory animals, and were approved by the Animal Care and Use Committees of the University of Ottawa and the University of Montreal. Three protocols were used, using rats 5 to 6 weeks of age.

**Protocol 1: High Salt Intake**

In male rats (n=8 to 12 per strain), the standard rat chow was replaced with rat chow containing 8% NaCl (1370 μmol of Na\(^+\)/g; Harlan Sprague Dawley). Tap water remained available ad libitum. Approximately 8 to 10 days after the start of the high-salt diet, in the afternoon under isoflurane inhalation, a polyethylene tubing (PE10 fused to PE50) was inserted into the abdominal aorta to measure BP the following morning in conscious rats (for more information, see the data supplement available online at http://hyper.ahajournals.org). One milliliter of blood was withdrawn for measurement of hematocrit and plasma electrolyte concentrations.

The rat was then anesthetized by isoflurane inhalation and mounted on a stereotaxic apparatus. A 23-gauge stainless steel cannula was inserted into the cisterna magna through a hole driven on the skull, and \(\sim150 \mu L\) of CSF was withdrawn at \(<5 \mu L/s\) for assessment of electrolyte concentration. Plasma and CSF Na\(^+\), K\(^+\), and Cl\(^-\) concentrations were measured by ion-selective electrodes on an LX20 PRO analyzer (Beckman Coulter, Inc.).

**Protocol 2: Brief Central Infusions of Na\(^+\)-Rich CSF**

A second set of male rats (n=7 to 8 per strain) remained on regular salt intake. Under isoflurane anesthesia, rats were mounted on a stereotaxic apparatus with a 23-gauge stainless steel cannula inserted just above the right lateral cerebroventricle as a guide cannula and fixed on the skull with dental cement. At least 5 days after the head surgery, the rats were reanesthetized with isoflurane, and the right femoral artery and jugular vein were cannulated with PE10/PE50 tubings, which were tunnelled to the back of neck. Through a flank incision, a pair of silver electrodes (A-M System, Inc) were then placed around and fixed to the left renal nerve with silicone rubber (SilGil 604, Wacker) and exteriorized as described previously.\(^{8}\)

At least 4 hours after recovery from the anesthesia in the original cage and after a 30-minute rest, baseline MAP, HR, and RSNA were recorded in resting, unrestrained animals for 20 minutes (see the data supplement). Subsequently, 4 icv infusions at 3.8 μL/min were performed (each for 8 minutes at 20-minute intervals) in the following sequence: CSF (146 mmol/L of Na\(^+\)) and Na\(^+\)-rich CSF containing 200, 300, and 450 mmol/L of Na\(^+\). Artificial CSF (aCSF)\(^{12}\) was used as vehicle. For icv infusion, a 26-gauge stainless steel was inserted into the guide cannula so that its tip protruded into the lateral ventricle. A 500-μL volume Hamilton microsyringe was used for icv infusion, mounted on a Sage 355 infusion pump. Five minutes before each infusion, the vasopressin \(V_1\) receptor antagonist D-(CH\(_2\))\(_5\)-Tyr-(Me)arginine vasopressin (30 μg/kg in 0.1 to 0.2 mL of saline; Sigma Chemical Co) was injected intravenously to exclude the effects of vasopressin release by the hypertonic saline.\(^{16}\) Intra-venous injection of the vasopressin antagonist did not affect resting MAP, RSNA, and HR.

**Protocol 3: Chronic Central Infusion of Na\(^+\)-Rich aCSF**

A third set of male rats (n=6 to 8 per strain) also remained on regular salt diet. Under isoflurane anesthesia, a telemetry BP probe (DSI model TA11PA-C40) was positioned intra-abdominally and secured to the ventral abdominal muscle with the catheter inserted into the lower abdominal aorta.\(^{1}\) The telemetry signal was processed using an analog adapter and computerized data acquisition system to calculate and store the mean values of BP and HR over a 1-minute interval every 30 minutes. Continuous recordings were started 2 days after the probe implantation. After recording for a 2- to 3-day control period, under isoflurane anesthesia, rats were mounted on a stereotaxic frame, and a 23-gauge, right-angled stainless steel cannula was implanted into the left lateral cerebral ventricle and fixed to the skull with acrylic cement.\(^{10}\) The cannula was placed 0.4 mm posterior and 1.4 mm lateral to the bregma. The lower end of the cannula was at a depth of 3.5 mm from the dura, and the upper end was connected to an osmotic minipump (model 2ML2, Alza) for chronic icv infusion at 5 μL/h for 14 days. The pumps were filled with aCSF containing 800 mmol/L of Na\(^+\) (Na\(^+\)-rich aCSF) and placed subcutaneously on the back of the rats. The rats returned to their original cages, and telemetry recording was continued for an additional 14 days. Icv infusion of Na\(^+\)-rich aCSF at this rate increases CSF [Na\(^+\)] by \(\sim5\) to 6 mmol/L.\(^{1,17}\)

At the end of the 14-day icv infusion, in the morning, rats were anesthetized with isoflurane, and PE50 catheters filled with heparinized saline (100 IU/mL) were placed in the left carotid artery and right jugular vein. At least 4 hours after the recovery for anesthesia, rats were placed in a small cage. After a 20-minute rest, baseline MAP and HR were recorded in resting animals for 5 minutes. Subsequently, the rat was blown twice on the face with a jet of air (2 pounds per square inch). Each lasted for 20 seconds with a 5-minute interval. After a 20-minute rest, phenylephrine (5 to 50 μg/min) was infused intravenously to obtain ramp increases of MAP by 50 mm Hg over 1 minute. Ten minutes after the responses had subsided, sodium nitroprusside (10 to 100 μg/min) was infused intravenously to obtain ramp decreases of MAP by 50 mm Hg over 1 minute. To evaluate the arterial baroreflex function, changes in HR in response to changes in MAP were analyzed as a logistic model.\(^{10}\)

**Data Analysis**

Responses of RSNA were expressed as percentages of resting values. For comparisons of responses to icv infusions in protocols 2 and 3, 1-way repeated-measures ANOVA was performed. When the F values were significant for main effect, a Duncan’s test was performed for multiple comparisons. Slopes of dose/Na\(^+\)-related MAP, RSNA, and HR responses to acute icv infusion of icv aCSF and Na\(^+\)-rich aCSF for each rat were calculated by linear regression. Student’s \(t\) test was performed to compare resting MAP and HR in corresponding strains on regular versus high salt intake. For other comparisons, 1-way ANOVA was used. Statistical significance was defined as \(P<0.05\).

**Results**

**Resting BP and HR on Regular and High Salt Intake**

Assessed by intra-arterial catheter (protocol 2), on regular salt intake, resting MAP and HR were \(\sim15\) mm Hg and \(\sim65\) bpm higher in Dahl S versus Lewis rats and \(\sim10\) mm Hg and \(\sim30\) bpm higher in C10S.L16 and C17S.L2 versus Lewis rats.
(P<0.05, for all). MAP and HR were significantly lower in C10S.L16 and C17S.L2 versus Dahl S rats (P<0.05; Figure 1, left). Assessed by telemetry (protocol 3), the MAP and HR in the night phase were significantly higher than those in daytime (data not shown). On regular salt intake, before chronic icv infusion of Na⁺-rich aCSF, the average 24-hour-MAP was ≈18 mm Hg higher in Dahl S versus Lewis rats, and ≈13 to 14 mm Hg higher in C10S.L16 or C17S.L2 versus Lewis rats. HR followed a similar pattern (Figure 2).

All of the rats developed normally over the 8 to 10 days of high salt intake. At the end of dietary period, there were no significant differences in gain of body weight (Table S1). After 8 to 10 days on high salt intake, resting MAP and HR were ≈40 mm Hg and ≈90 bpm higher in Dahl S versus Lewis rats, and ≈25 mm Hg and ≈65 bpm higher in C10S.L16 and C17S.L2 versus Lewis rats, respectively. Compared with values on regular salt, high salt intake did not change MAP in Lewis rats, increased MAP by ≈20 mm Hg in C10S.L16 and C17S.L2, and by ≈30 mm Hg in Dahl S rats (Figure 1).

**CSF and Plasma Electrolytes on High Salt Intake**

After a high-salt diet for 8 to 10 days, CSF [Na⁺] was ≈5 mmol/L higher in Dahl S, C10S.L16, and C17S.L2 versus Lewis rats. There was no significant difference in CSF [Na⁺] among Dahl S, C10S.L16, and C17S.L2 rats (Figure 3). No significant differences in CSF [Na⁺] among the 4 strains were detected (data not shown). CSF [Cl⁻] tended to be higher in Dahl S, C10S.L16, and C17S.L2 rats compared with Lewis rats (123±1, 124±2, and 123±2 mmol/L versus 121±1 mmol/L; P=0.2). There were no significant differences in plasma concentrations of Na⁺, K⁺, and Cl⁻ and hematocrit among the 4 groups of rats (Table S1).

**Responses to Brief icv Infusion of Na⁺-Rich aCSF**

Infusion (icv) of aCSF did not change resting MAP, HR, and RSNA. In contrast, icv infusion of Na⁺-rich aCSF with the 3 concentrations of Na⁺ caused parallel increases in MAP, RSNA, and HR. The extent of maximal MAP, RSNA, and HR responses to icv infusions was related to the [Na⁺] in the aCSF (Figure 4). Responses to icv infusion of Na⁺-rich aCSF...
were 80% to 100% larger in Dahl S and C17S.L2 versus Lewis rats and 35% to 40% larger in C10S.L16 versus Lewis rats. Responses to icv infusion of Na⁺-rich aCSF containing 200, 300, and 450 mmol/L Na⁺ in Lewis, C10S.L16 (C10), C17S.L2 (C17), and Dahl S rats on regular salt intake. Data are mean±SE (n=8 per strain). *P<0.05 vs others; a, P<0.05 vs Lewis rats.

were 80% to 100% larger in Dahl S and C17S.L2 versus Lewis rats and 35% to 40% larger in C10S.L16 versus Lewis rats. Responses to icv infusion of Na⁺-rich aCSF with 300 and 450 mmol/L Na⁺ were significantly smaller in C10S.L16 versus Dahl S and C17S.L2 rats (Figure 3). There were no significant differences in responses to icv infusion of Na⁺-rich aCSF between Dahl S and C17S.L2. The slopes of responses to icv infusion of Na⁺-rich aCSF were steeper in Dahl S and C17S.L2 versus Lewis rats. In C10S.L16 rats, the slopes were flatter versus Dahl S and C17S.L2 but steeper versus Lewis rats (Table S2).

**Responses to Chronic icv Infusion of Na⁺-rich aCSF**

**MAP and HR**

MAP started to increase in the first night after start of the infusion. The average 24-hour MAP reached peak levels at days 3 to 4 and then declined slightly (Figure 2). During icv infusion, average 24-hour MAP was significantly lower in Lewis rats versus others and in C10S.L16 versus C17S.L2 or Dahl S rats. MAP tended to be lower in C17S.L2 versus Dahl S rats (P=0.07). At days 4 and 14, in Lewis and C10S.L16 rats, the absolute and percentage increases in MAP relative to control levels were similar and significantly less than those in C17S.L2 or Dahl S rats (Figure 5). The absolute and percentage increases of MAP were similar in C17S.L2 and Dahl S rats. Icv infusion of Na⁺-rich aCSF increased the difference between nighttime versus daytime MAP, similarly for the 4 strains (≈4 to 5 mm Hg at day −1, ≈7 to 9 mm Hg at day 4, and ≈8 to 10 mm Hg at day 14).

HR also started to increase during the first night of infusion, reached peak levels at days 2 to 3, and then declined gradually. HR remained significantly lower in Lewis rats versus others and in C10S.L16 versus C17S.L2 and Dahl S rats and was fairly similar in C17S.L2 and Dahl S rats. At days 3 and 14, absolute increases in HR were significantly less in Lewis versus C10S.L16, C17S.L2, and Dahl S rats (day 3: 38±4 versus 59±4, 58±6, and 54±6 bpm; P<0.05). However, percentage increases in HR did not differ among the 4 groups (day 3: +8±2%, +11±3%, +10±2%, and +10±1%; P not significant). Differences between nighttime and daytime HR were similar among the 4 strains (≈30 bpm at day 3) and were not affected by the icv infusion.

**Responses to Air Stress and Arterial Baroreflex Function**

Expressed as either absolute increases or percentages of resting values, MAP and HR were similarly increased by air stress in Lewis and C10S.L16 rats. In C17S.L2 and Dahl S rats, increases in MAP and HR by air stress were similar and were significantly enhanced compared with Lewis and C10S.L16 rats (Table). As indicated by the maximum and average slopes and range of
HR changes, after a 2-week infusion of Na⁺-rich aCSF, baroreflex control of HR tended to be less in C10S.L16 versus Lewis rats. Baroreflex control of HR was similar in C17S.L2 and Dahl S rats and was clearly impaired compared with Lewis and C10S.L16 rats.

**Discussion**

The major new findings of the present study are as follows: (1) on a high-salt diet for 8 to 10 days, CSF [Na⁺] is similarly higher (≈5 mmol/L) in Dahl S and the 2 congenic strains C10S.L16 and C17S.L2, but BP increases by ≈30 mm Hg in Dahl S rats and ≈20 mm Hg in C10S.L16 and C17S.L2 rats; (2) on regular salt sympathetic and BP responses to brief icv infusion of Na⁺-rich aCSF are 1-fold larger in Dahl S and C17S.L2 and 30% to 40% larger in C10S.L16 versus Lewis rats; and (3) chronic icv infusion of Na⁺-rich aCSF causes significantly larger increases in resting BP, enhances BP and HR responses to air stress, and impairs baroreflex function in Dahl S and C17S.L2 but not C10S.L16 rats compared with Lewis rats. In other words, the alleles of C10QTL2 but not of C17QTL from Lewis rats are able to decrease these functions.

HR changes, after a 2-week infusion of Na⁺-rich aCSF, baroreflex control of HR tended to be less in C10S.L16 versus Lewis rats. Baroreflex control of HR was similar in C17S.L2 and Dahl S rats and was clearly impaired compared with Lewis and C10S.L16 rats.

Chronic infusion similar to the responses in Lewis rats. Sympathoexcitatory responses showed a similar pattern. Because resting BPs are rather similar in the 2 congenic strains, this difference in responsiveness to CSF [Na⁺]↑ is clearly not somehow because of different hypertension levels. After a 2-week icv infusion of Na⁺-rich aCSF, C17S.L2 and Dahl S rats showed similarly enhanced responses to air stress and similar impairment of arterial baroreflex. These changes were absent in C10S.L16. Therefore, it appears that genetic variants in C10QTL2 but not C17QTL contribute to the phenotype of enhanced sympathoexcitatory and pressor responses to CSF [Na⁺]↑ in Dahl S rats.

Sympathoexcitatory and pressor responses to CSF [Na⁺]↑ are mediated via CNS pathways involving mineralocorticoid receptor, ENaC, ouabain, and angiotensin type 1–receptor stimulation. Central responses to ouabain and Ang II are not enhanced in Dahl S rats, suggesting that the primary dysregulation is more proximal. The results obtained in C10S.L16 rats suggest that variants in genes located on C10QTL2 enhance sympathoexcitatory and pressor responses to CSF [Na⁺]↑ in Dahl S rats. In rats, genes for α-, β-, and γ-ENaC are located on chromosome 4q42 and chromosome 1q36–q41, and in Dahl S rats no biologically relevant gain-of-function mutations in coding and promoter sequences of ENaC subunits have been found. Genes regulating ENaC activity, such as the ubiquitin–protein ligase Nedd4-2 and serum glucocorticoid inducible kinase (sgk-1), the genes for aldosterone synthase, CYP11B2, for mineralocorticoid receptor and corticosterone-inactivating enzyme 11β-HSD-2, and other known steroid-metabolizing enzymes are also not found on chromosome 10. The voltage-dependent calcium channel y4 subunit, cacng4, is expressed primarily in the rodent brain and plays a role in neuronal excitation. Cacng4 is 1 of the genes located in the interval harboring C10QTL2, and further studies are needed to explore whether possible variants of cacng4 contribute to increased neuronal responsiveness to Na⁺ in Dahl S rats.

In Dahl S rats, high salt intake for 1 week increases average 24-hour MAP by ≈15 mm Hg measured by telemetry. In the present study, icv infusion of Na⁺-rich aCSF for 1 week also increased 24-hour MAP by ≈15 mm Hg in Dahl S rats and by only ≈7 mm Hg in Lewis rats. Because high salt intake in
Dahl S rats and icv infusion of Na\(^+\)-rich aCSF at the rate used increases CSF [Na\(^+\)] to similar extent (5 to 6 mmol/L), it appears that, in Dahl S rats, in the early stage of high salt intake, the 5- to 6-mmol/L increase in CSF [Na\(^+\)] may count for the \(\approx 7\) mm Hg increase in resting MAP and increased responsiveness and blunting of arterial baroreflex function versus Dahl R, Wistar, or Lewis rats for an additional \(\approx 8\)-mm Hg increase. The absence of this second component in the C10S.L16 may explain the \(\approx 10\)-mm Hg lower MAP in this strain after 1 week on high salt intake. On the other hand, both CNS components are similar in Dahl S and C17S.L2, but BP increases less in C17S.L2 on high salt intake. This finding indicates that genes located on C17QTL affect the BP response to high salt intake through other mechanisms rather than influencing CSF [Na\(^+\)] or responses to CSF [Na\(^+\)] \(\uparrow\). These are unlikely mechanisms downstream to the CNS, because these would have affected responses to CSF [Na\(^+\)]. BP responses to high salt intake in Dahl S rats are determined by both renal and nonrenal (eg, CNS) mechanisms, and each is sufficient to produce hypertension on high salt intake, but the 2 together appear to cause more severe hypertension. In the C17S.L2 congenic strain, peripheral non-CNS (eg, renal) mechanisms may be affected, leading to a lower BP on high salt intake despite persistence of enhanced activity of the CNS mechanisms.

A limitation of the present study is that CSF [Na\(^+\)] was measured in the 4 strains only on high salt intake. The observed values are consistent with previously reported findings that high salt intake increases CSF [Na\(^+\)] in Dahl S (and presumably, therefore, also the 2 congenic strains) but not Dahl R rats and Wistar (and presumably also not in Lewis) rats.

**Perspectives**

The present findings suggest that, in Dahl S rats, genetic variants within C10QTL2 on chromosome 10 contribute to gain-of-function of central mechanisms determining neuronal responses to CSF [Na\(^+\)] \(\uparrow\). Further studies in substrains containing fewer genes need to be carried out to identify the gene(s) responsible for this neuronal phenotype. Various genetic approaches are available, such as mutation screenings, fine congenic resolution, transgenesis, and gene targeting.

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**Disclosures**

None.

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