Effects of Chronic Intraventricular Sodium on Blood Pressure and Fluid Balance

Yuhei Kawano, R. Takashi Sudo, and Carlos M. Ferrario

To examine if chronic sodium loading on the brain produces sustained increases in blood pressure, water intake, and sodium excretion, hypertonic (0.5 M and 1.5 M) and isotonic (0.15 M) NaCl solutions were infused into the third ventricle of Sprague-Dawley rats at a rate of 5.5 μl/hr for 7 days. Intracerebroventricular infusion of 1.5 M NaCl significantly increased systolic blood pressure during the entire infusion period (+23±5 mm Hg on day 1 and +15±2 mm Hg on day 7, n=10, mean±SEM). Blood pressure rose insignificantly in the 0.5 M NaCl group, whereas it remained at the baseline levels in the 0.15 M NaCl group. The increases in water intake (day 2), positive water balance (day 2), and negative sodium balance (day 3) were observed in the 1.5 M NaCl group. On day 7, the 1.5 M NaCl group showed hyponatremia and low plasma osmolality and had higher plasma norepinephrine but not vasopressin compared with the 0.15 M NaCl group. In another series of study, depressor response to intravenous hexamethonium (20 mg/kg) in the 1.5 M NaCl group was greater than that in the 0.15 M NaCl group on both day 1 and 7. The depressor response to d(CH2)3Tyr(Me)-arginine vasopressin (10 μg/kg) in the 1.5 M NaCl group was greater on day 1 but not on day 7. These results indicate that sustained sodium stimulus on the central nervous system causes mild hypertension and alters water and sodium balance. The sympathetic nervous system but not vasopressin may play an important role in the chronic phase of central NaCl-induced hypertension. (Hypertension 1991;17:28-35)

Hypertonic NaCl administered into the central nervous system influences cardiovascular and body fluid conditions by producing blood pressure elevation, tachycardia, drinking response, and natriuresis.1-5 These events are accompanied by various neurohormonal changes such as stimulation of the sympathetic nervous system with suppression of the renal nerve activity, release of vasopressin, sodium pump inhibitor and atrial natriuretic factor, stimulation of the pituitary-adrenocortical axis, and suppression of the peripheral renin-angiotensin system.1,3,5-8 Both the sympathetic nervous system and vasopressin appear to mediate the pressor response to intracerebroventricularly administered hypertonic NaCl.5,9

The central action of sodium might play an important role in the relation between salt and hypertension. The sympathetic nervous system and vasopressin may participate in several models of salt-dependent hypertension such as deoxycorticosterone (DOC)-salt hypertension10,11 and Dahl salt-sensitive rats.12-13 Electrical lesion of the anteroventral third ventricle area in the forebrain can prevent or attenuate these models of hypertension as well as pressor response to intracerebroventricular infusion of hypertonic NaCl.14-16

Although the central effects of hypertonic NaCl are well documented in acute experiments, there are few chronic studies. Miyajima and Bunag17 reported that intracerebroventricular infusion of hypertonic NaCl for 11 days caused mild hypertension and reduced depressor response to anterior hypothalamic stimulation in rats. They also observed that impairment of the baroreceptor reflex preceded the rise in blood pressure.18 However, the mechanisms of blood pressure elevation during chronic intracerebroventricular infusion of hypertonic NaCl has not been fully understood. It is not known how chronic sodium stimulus on the brain affects the body fluid balance.

To determine whether long-term administration of hypertonic NaCl into the central nervous system produces sustained increases in blood pressure, water intake, and sodium excretion, we studied effects of a 7-day intracerebroventricular infusion of hypertonic NaCl on blood pressure and water and sodium balance in rats. The second aim of this study was to
examine neurohormonal mechanisms in the maintenance of blood pressure during chronic intracerebroventricular infusion of hypertonic NaCl.

**Methods**

**Animal Preparation**

Seventy-three male Sprague-Dawley rats weighing 200–250 g were studied in strict adherence to the Guide for the Care and Use of Laboratory Animals published by the National Institutes of Health in 1985. The rats were given regular rat chow (Ralston Purina, St. Louis, Mo.), which contained 177 meq/kg Na+, and tap water. The cage room was maintained at constant temperature (23°C) and humidity (55%) with a 12-hour light/dark cycle.

Intracerebroventricular cannulation was performed in 66 rats. The rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.) and were placed in a stereotaxic apparatus (David Kopf Instruments, Tujunga, Calif.). After the skull was exposed and leveled between the bregma and lambda, a small hole was drilled at a point 0.5 mm posterior from the bregma. An L-shaped, 23-gauge stainless cannula was lowered into the third ventricle; usually the position was 5.5 mm below the surface of the skull. The correct location of the cannula tip was assessed by observing free movement of saline column in a PE-50 tubing (Clay Adams, Parsippany, N.J.) connected to the cannula. The location was also verified by injection of Evans blue dye at the end of the experiment. After the cannula was secured to the skull with dental cement and small screws, it was connected to an osmotic minipump (model 2002, Alza Corp., Palo Alto, Calif.) with a PE-50/60 combination tubing. The minipump was filled with sterile isotonic (0.15 M) saline and was placed subcutaneously in the animal’s back. A small amount of saline (0.5 μl/hr) was continuously delivered to avoid occlusion of the cannula during the recovery and control period.

In another group of seven rats, a PE-60 catheter was inserted into the jugular vein while the rat was under pentobarbital anesthesia. The catheter was also connected to the osmotic minipump (model 2002, Alza) and filled with heparinized saline to avoid clot formation.

At the end of the surgical procedure, the rats were given penicillin G (20,000 units) and streptomycin (25 mg) for prophylactic purposes. Eight rats were excluded from the study because of failure of the cannula or the tubing at the end of the experimental period.

**Study 1**

Thirty rats with intracerebroventricular cannulas and seven rats with intravenous catheters were housed individually in metabolic cages. The rats were given powdered regular rat chow and tap water. After a 4-day period for recovery from the surgical procedure and for accommodation, control measurements were carried out for 3 days. The rats were then subjected to replacement of the osmotic minipumps. Under light methoxyflurane anesthesia, the used pumps and tubes were taken out, and new osmotic pumps (model 2ML2, Alza) and tubes filled with various concentrations of NaCl solution were connected to the intracerebroventricular cannulas. This procedure was used to minimize surgical invasion when intracerebroventricular infusions of hypertonic NaCl were begun. The concentrations of administered NaCl solutions were 0.15 M (n=10), 0.5 M (n=10), and 1.5 M (n=10). In the other seven rats, 1.5 M NaCl was administered intravenously by the replaced minipumps. The estimated infusion rate of the new osmotic pump was 5.5 μl/hr lasting for 14 days. The rate was confirmed by measurement of remaining volume in the pumps after 7 days, and the concentration of the NaCl solutions remained constant.

Measurements of systolic blood pressure, heart rate, body weight, amounts of food and water intake, and urine volume were performed for 3 days during the control period and for 7 days after the pump replacement. Systolic blood pressure and heart rate were measured every other day by tail-cuff plethysmography with pneumatic pulse transducer (Narco BioSystems, Houston, Tex.). The other variables were measured every day. Aliquots of urine samples were stored at −20°C for determination of Na+ concentration. On the seventh day, the rats were killed by decapitation. Trunk blood was collected into heparinized tubes, and plasma was rapidly separated for determination of Na+, osmolality, vasoressin, and plasma renin activity (PRA).

**Study 2**

Twenty-eight rats with intracerebroventricular cannulas were housed in ordinary cages and were given the regular rat chow and tap water ad libitum. Just as in the metabolic study, the new osmotic pumps (model 2ML2, Alza) filled with 0.15 M or 1.5 M NaCl were implanted 1 week after the first surgery. Continuous intracerebroventricular infusions (5.5 μl/hr) were carried out for 1 day (0.15 M, n=6; 1.5 M, n=6) or for 7 days (0.15 M, n=7; 1.5 M, n=9).

On day 1 or day 7, PE-50 catheters were inserted into the carotid artery and jugular vein under light anesthesia with methoxyflurane. At least 3 hours later, the conscious animals were placed in a plastic holder for direct measurement of blood pressure and blood sampling. Arterial blood pressure was measured using a solid-state transducer (MP-15, Micron Instruments, Los Angeles, Calif.) and was recorded on an ink writing recorder (Gould Inc., Cleveland, Ohio). Thirty minutes after starting blood pressure measurement, 1 ml arterial blood was sampled for determination of plasma catecholamines. The amount of withdrawn blood was replaced with isotonic saline. After the blood sampling, three succeeding intravenous injections were given at 5-minute intervals. First, 20 mg/kg hexamethonium chloride (United States Biochemical Corp., Cleveland, Ohio), a ganglionic blocker, was given to evaluate the neural...
contribution to maintenance of blood pressure. Second, d(CH2)5Tyr(Me)-arginine vasopressin (Bachem Inc., Torrance, Calif.), a vasopressin antagonist, was administered at a dose of 10 µg/kg to block vasoconstrictive action of vasopressin. Finally, 2 mg/kg captopril (E.R. Squibb & Sons, Inc., Princeton, N.J.), an angiotensin converting enzyme inhibitor, was given to assess the role of the renin-angiotensin system.

After the measurement of blood pressure, five rats of the 7-day intracerebroventricular 0.15 M NaCl group and five rats of the 7-day intracerebroventricular 1.5 M NaCl group were anesthetized again with sodium pentobarbital. The rats were placed in a stereotaxic apparatus, and the atlantooccipital membrane was exposed through a midline incision. Then, cerebrospinal fluid (CSF) was collected from the cisternal magna by puncturing the atlanto-occipital membrane with a 27-gauge needle. The CSF samples were stored at -20°C until the determination of Na+ concentration.

Biochemical Measurements and Data Analysis

Concentrations of Na+ in the plasma, urine, and CSF were measured by flame photometry (model 343, Instrumentation Laboratories, Lexington, Mass.). Osmolality was measured by freezing point method (model 3D2, Advanced Instruments, Needham Heights, Mass.). Plasma vasopressin11 and PRA19 were determined by radioimmunoassay. Concentrations of norepinephrine and epinephrine were assayed by radioenzymatic method.20

All data were expressed as mean±SEM. Statistical analysis was performed by two-way analysis of variance and subsequent Tukey's multiple comparison test. Comparisons between groups were also made using Student's t test when appropriate. A value of p<0.05 was considered statistically significant.

Results

In the control period, systolic blood pressure was 117.5±2.9 mm Hg in the intracerebroventricular 1.5 M NaCl group, 119.9±2.8 mm Hg in the 0.5 M NaCl group, and 120.1±2.5 mm Hg in the 0.15 M NaCl group. The control data were average values measured in the 3-day period and were not different among the three groups. During the 7 days of the intracerebroventricular infusion period, the rats given 1.5 M NaCl showed significant increases in systolic blood pressure (Figure 1). The changes were +22.7±5.1 mm Hg on day 1 and +15.0±2.3 mm Hg on day 7 (p<0.05). Systolic blood pressure rose insignificantly in the 0.5 M NaCl group (+8.6±2.8 mm Hg on day 7), whereas it remained at the baseline level in the control (0.15 M NaCl) group. Heart rate did not change significantly in any of these groups. In the group of intravenous 1.5 M NaCl, systolic blood pressure did not change during the infusion period (Table 1).

Body weight increased on day 7 in the groups of intracerebroventricular 1.5 M, 0.5 M, and 0.15 M NaCl (Table 2). However, the growth in the 1.5 M NaCl group was smaller than that in the 0.15 M NaCl group (p<0.05). As a result of surgical stress, decreases in food intake were seen in all groups on day 1. Amount of water intake increased in the 1.5 M NaCl group on day 3, but it did not change significantly in the other two groups. Urine volume increased in the 1.5 M NaCl group on day 5 and 7, but it decreased in the control group on day 1. Urinary Na+ excretion reduced significantly during the initial 2 days of the intracerebroventricular infusion period in all groups. Then it increased in the 1.5 M NaCl group on days 3 and 5 and in the 0.5 M NaCl group on day 3, but not in the control group.

Water and Na+ balance were calculated by differences between daily intake (oral intake plus intracerebroventricular infusion) and urinary output. The water balance became positive in the 1.5 M NaCl group on day 3 (+5.8±1.7 ml) and in the 0.5 M NaCl group on day 2 compared with the control level, but it did not change significantly in the 0.15 M NaCl group (Table 2). The sodium balance became positive in the control group on days 1 and 2 and in the

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Day 1</th>
<th>Day 3</th>
<th>Day 5</th>
<th>Day 7</th>
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<tbody>
<tr>
<td>SBP (mm Hg)</td>
<td>121±3</td>
<td>121±4</td>
<td>122±3</td>
<td>125±4</td>
<td>124±4</td>
</tr>
<tr>
<td>HR (beats/min)</td>
<td>395±13</td>
<td>411±16</td>
<td>410±12</td>
<td>414±6</td>
<td>411±10</td>
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</tbody>
</table>

*Values given are mean±SEM. SBP, systolic blood pressure; HR, heart rate.
TABLE 2. Body Weight, Food and Water Intake, Urine Volume, Urinary Sodium Excretion, and Water and Sodium Balance During 7 Days of Intracerebroventricular Infusions of 1.5 M, 0.5 M, and 0.15 M NaCl

<table>
<thead>
<tr>
<th>Variables</th>
<th>Infusion</th>
<th>Control</th>
<th>Day 1</th>
<th>Day 2</th>
<th>Day 3</th>
<th>Day 4</th>
<th>Day 5</th>
<th>Day 6</th>
<th>Day 7</th>
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</thead>
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<tr>
<td>Body weight (g)</td>
<td>1.5 M</td>
<td>252±13</td>
<td>248±12</td>
<td>250±13</td>
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<td>255±13</td>
<td>256±13</td>
<td>258±13</td>
<td>259±13*</td>
</tr>
<tr>
<td></td>
<td>0.5 M</td>
<td>262±7</td>
<td>266±8</td>
<td>265±8</td>
<td>267±8</td>
<td>269±8*</td>
<td>272±8*</td>
<td>275±8*</td>
<td>276±8*</td>
</tr>
<tr>
<td></td>
<td>0.15 M</td>
<td>275±12</td>
<td>270±11</td>
<td>271±11</td>
<td>277±11</td>
<td>279±11</td>
<td>282±11*</td>
<td>287±11*</td>
<td>291±11*</td>
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<tr>
<td>Food intake (g/day)</td>
<td>1.5 M</td>
<td>21.2±1.1</td>
<td>16.4±0.6*</td>
<td>19.7±0.7</td>
<td>20.4±0.8</td>
<td>20.0±1.2</td>
<td>21.6±1.0</td>
<td>20.4±0.9</td>
<td>21.6±1.2</td>
</tr>
<tr>
<td></td>
<td>0.5 M</td>
<td>20.8±0.5</td>
<td>17.9±0.6*</td>
<td>21.2±0.7</td>
<td>21.9±0.9</td>
<td>22.5±0.9*</td>
<td>22.6±0.6*</td>
<td>22.1±1.0</td>
<td>23.9±1.1*</td>
</tr>
<tr>
<td></td>
<td>0.15 M</td>
<td>21.8±1.1</td>
<td>17.4±1.2*</td>
<td>21.1±1.1</td>
<td>22.9±1.1</td>
<td>22.9±1.1</td>
<td>22.6±1.4</td>
<td>22.9±1.5</td>
<td>24.5±1.1*</td>
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<tr>
<td>Water intake (ml/day)</td>
<td>1.5 M</td>
<td>37.1±2.0</td>
<td>42.8±2.4</td>
<td>46.8±3.6*</td>
<td>41.7±2.9</td>
<td>45.0±3.4</td>
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<td>44.0±3.8</td>
<td>42.9±3.4</td>
</tr>
<tr>
<td></td>
<td>0.5 M</td>
<td>37.2±2.0</td>
<td>40.2±1.9</td>
<td>42.4±3.5</td>
<td>42.1±3.5</td>
<td>44.2±2.9</td>
<td>42.0±2.7</td>
<td>41.1±2.5</td>
<td>43.9±2.6</td>
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<tr>
<td></td>
<td>0.15 M</td>
<td>38.7±2.8</td>
<td>36.0±2.3</td>
<td>41.3±2.7</td>
<td>44.8±3.4</td>
<td>42.1±1.8</td>
<td>39.0±3.3</td>
<td>40.8±2.8</td>
<td>42.3±2.8</td>
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<tr>
<td>Urine volume (ml/day)</td>
<td>1.5 M</td>
<td>17.4±0.7</td>
<td>19.2±2.1</td>
<td>20.9±3.4</td>
<td>21.4±1.7</td>
<td>23.5±2.3</td>
<td>28.5±4.2*</td>
<td>23.4±3.6</td>
<td>24.1±2.6*</td>
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<tr>
<td></td>
<td>0.5 M</td>
<td>17.5±1.2</td>
<td>14.9±1.1</td>
<td>19.1±2.7</td>
<td>22.7±3.7</td>
<td>20.0±2.3</td>
<td>23.4±2.5*</td>
<td>19.9±1.9</td>
<td>23.8±2.7</td>
</tr>
<tr>
<td></td>
<td>0.15 M</td>
<td>18.5±1.0</td>
<td>14.2±0.9*</td>
<td>17.4±1.5</td>
<td>21.4±1.1</td>
<td>19.8±1.1</td>
<td>20.3±1.5</td>
<td>18.8±1.1</td>
<td>20.4±1.1</td>
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<tr>
<td>Urinary Na (meq/day)</td>
<td>1.5 M</td>
<td>2.9±0.2</td>
<td>1.7±0.3*</td>
<td>2.2±0.2*</td>
<td>3.4±0.2*</td>
<td>3.0±0.3</td>
<td>3.5±0.3*</td>
<td>3.1±0.3</td>
<td>3.1±0.2</td>
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<tr>
<td></td>
<td>0.5 M</td>
<td>2.8±0.2</td>
<td>1.6±0.2*</td>
<td>2.5±0.2</td>
<td>3.3±0.2*</td>
<td>3.0±0.2</td>
<td>3.2±0.2</td>
<td>2.7±0.2</td>
<td>3.1±0.2</td>
</tr>
<tr>
<td></td>
<td>0.15 M</td>
<td>3.2±0.2</td>
<td>1.4±0.2*</td>
<td>2.6±0.3*</td>
<td>3.5±0.2</td>
<td>3.3±0.2</td>
<td>3.5±0.3</td>
<td>3.1±0.3</td>
<td>3.4±0.2</td>
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<tr>
<td>Water balance (ml/day)</td>
<td>1.5 M</td>
<td>19.7±1.6</td>
<td>23.6±1.7</td>
<td>25.9±2.0*</td>
<td>20.3±2.0</td>
<td>21.5±1.8</td>
<td>17.1±1.9</td>
<td>20.6±1.8</td>
<td>18.8±2.1</td>
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<tr>
<td></td>
<td>0.5 M</td>
<td>19.7±1.3</td>
<td>25.3±1.9*</td>
<td>23.5±2.0</td>
<td>19.4±1.7</td>
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<td>0.15 M</td>
<td>20.2±2.1</td>
<td>21.8±1.8</td>
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<td>18.7±1.9</td>
<td>22.0±1.3</td>
<td>21.9±2.1</td>
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<tr>
<td>Na balance (meq/day)</td>
<td>1.5 M</td>
<td>0.7±0.1</td>
<td>1.1±0.3</td>
<td>1.1±0.2</td>
<td>0.0±0.1*</td>
<td>0.4±0.1</td>
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<td>0.4±0.2</td>
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<tr>
<td></td>
<td>0.5 M</td>
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<tr>
<td></td>
<td>0.15 M</td>
<td>0.5±0.2</td>
<td>1.5±0.1*</td>
<td>1.0±0.2</td>
<td>0.3±0.2</td>
<td>0.6±0.2</td>
<td>0.3±0.1</td>
<td>0.8±0.3</td>
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</table>

Values are mean±SEM.
*p<0.05 vs. control; tp<0.05 vs. 0.15 M group.

0.5 M NaCl group on day 1. Conversely, negative Na⁺ balance was observed in the 1.5 M NaCl group on day 3 (-0.6±0.2 meq). The sum of changes in Na⁺ balance during the 7-day period in the 1.5 M NaCl group was also negative (-1.7±0.7 meq, p<0.05) and was significantly different from that in the control group (2.0±1.3 meq).

After the 7-day intracerebroventricular infusion, the hypertonic NaCl groups had lower plasma Na⁺ and osmolality than the control group (Figure 2). The levels were significantly different between the 1.5 M NaCl and the 0.15 M NaCl group (Na⁺, 138.2±1.2 versus 142.4±1.7 meq/l; osmolality, 283.3±3.3 versus 292.1±3.3 mOsm/kg). The three groups had almost identical plasma vasopressin levels (3.1±0.3 pg/ml in the 1.5 M NaCl group, 3.0±0.8 pg/ml in the 0.5 M NaCl group, and 2.9±0.5 pg/ml in the control group). There were no significant differences in PRA among the groups, although it tended to be lower in the hypertonic NaCl groups.

Table 3 shows concentrations of Na⁺ and K⁺ in the cisternal CSF after 7 days of intracerebroventricular infusion of 1.5 M and 0.15 M NaCl. The 1.5 M NaCl group had higher CSF Na⁺ than the control group, and the average difference between the groups was

![Figure 2](http://hyper.ahajournals.org/)

**Figure 2.** Bar graphs showing plasma levels of sodium (Na⁺), osmolality (Osm), vasopressin (VP), and plasma renin activity (PRA) at the end of 7 days of intracerebroventricular infusions of 1.5 M, 0.5 M, and 0.15 M NaCl. *p<0.05 vs. 0.15 M NaCl.
TABLE 3. Sodium and Potassium Concentrations in Cerebrospinal Fluid After 7 Days of Intracerebroventricular Infusions of 1.5 M and 0.15 M NaCl

<table>
<thead>
<tr>
<th>Infusion</th>
<th>Na (meq/l)</th>
<th>K (meq/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.5 M NaCl</td>
<td>153.2±0.7*</td>
<td>3.0±0.2</td>
</tr>
<tr>
<td>0.15 M NaCl</td>
<td>148±0.5</td>
<td>3.1±0.2</td>
</tr>
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</table>

*p<0.05 between the groups.

4.8 meq/l. There was no difference in the CSF K+ between the two groups.

Figure 3 shows plasma levels of norepinephrine and epinephrine in groups of rats that were given intracerebroventricular infusion of 1.5 M and 0.15 M NaCl for 1 day or 7 days. Plasma norepinephrine in the intracerebroventricular 1.5 M NaCl groups was higher than that in the 0.15 M NaCl groups (day 1, 657±68 versus 492±58 pg/ml; day 7, 610±57 versus 452±48 pg/ml, p<0.05). Plasma epinephrine was also higher in the hypertonic NaCl groups, although it was not statistically significant.

Levels of mean blood pressure in the intracerebroventricular 1.5 M and 0.15 M NaCl groups before and after pharmacological interventions are shown in Figure 4. The 1.5 M NaCl groups had higher mean blood pressure than the control groups (day 1, 141.0±2.2 versus 118.0±3.0 mm Hg; p<0.001; day 7, 133.8±2.5 versus 124.0±1.7 mm Hg; p<0.05). Intravenously administered hexamethonium produced greater depressor responses in the hypertonic NaCl groups than the control groups both on day 1 (−62.7±4.1 versus −49.3±4.4 mm Hg; p<0.05) and day 7 (−64.5±3.8 versus −53.0±4.4 mm Hg; p<0.05) and abolished the difference in blood pressure between the groups on day 7. Subsequent intravenous administration of d(CH2)5Tyr(Me)-arginine vasopressin caused a greater fall in blood pressure in the 1.5 M NaCl group than in the control group (−10.7±2.5 versus −4.0±1.5 mm Hg; p<0.05) and eliminated the pressure difference on day 1. However, the vasopressin antagonist reduced blood pressure similarly in the two groups on day 7. Finally, captopril produced comparable blood pressure reductions in the 1.5 M and 0.15 M NaCl groups both on day 1 and day 7.

Discussion

In this study, a 7-day infusion of 1.5 M NaCl into the third ventricle of rats at a rate of 5.5 μl/hr elevated blood pressure throughout the infusion period. This change was not observed in the intracerebroventricular 0.15 M NaCl group.
broventricular isotonic NaCl group or in the intraventricular hypertonic NaCl group, indicating the effect of hypertonic NaCl was due to its action on the central nervous system. Our results confirm the findings of a few previous studies. Miyajima and Bunag showed that third ventricular infusion of 0.8 M NaCl at the same infusion rate for 11 days elevated blood pressure in rats. Katahira et al. also observed that chronic administration of 1.5 M NaCl into the lateral ventricle of rats caused a moderate increase in blood pressure. Therefore, a chronic increase in NaCl concentration in the central nervous system is able to produce sustained blood pressure elevation.

The dose-related effects of chronic intracerebroventricular infusion of NaCl on blood pressure are not well-known. In our study, only the intracerebroventricular infusion of 1.5 M NaCl, which delivered 0.2 meq/day Na+ (about 6% of dietary Na+ intake), produced significant and sustained blood pressure elevation. However, the increases in blood pressure were modest as in the previous studies. The lower concentration (0.5 M) of NaCl caused insignificant blood pressure elevation. In our preliminary study, the higher concentrations (2.5 M and 4.0 M) of NaCl failed to produce sustained hypertension but had toxic effects since many rats did not survive until the end of the infusion period (unpublished data from our laboratory). The NaCl stimulus, restricted to the brain, may not be enough to produce severe hypertension in normal rats.

The pressor response to intracerebroventricular infusion of hypertonic NaCl appears to be mediated by both the sympathetic nervous system and vasopressin in acute experiments. Although there were few chronic studies, Miyajima and Bunag observed that the sympathoinhibitory response to electrical stimulation of the anterior hypothalamus was reduced and the depressor response to intravenous administration of pentolinium was augmented in the rats given chronic intracerebroventricular infusion of hypertonic NaCl. In our study, mild hypertension induced by chronic intracerebroventricular infusion of NaCl was accompanied by elevated plasma catecholamine levels and augmented depressor response to ganglionic blockade with intravenous administration of hexamethonium both at the early (day 1) and chronic (day 7) phase. Our results support the role of the sympathetic nervous system in the hypertension induced by chronic intracerebroventricular infusion of hypertonic NaCl.

However, the role of vasopressin in the blood pressure elevation may be different between the early and chronic phase of intracerebroventricular NaCl infusion. The depressor response to an antipressor antagonist of vasopressin in the intracerebroventricular hypertonic NaCl group was greater than that in the control group on day 1 but not on day 7. Plasma vasopressin level was not different between the groups after the 7-day infusion. These findings suggest that vasopressin may contribute to blood pressure elevation in the early phase of chronic intracerebroventricular hypertonic NaCl infusion, but its role appears to diminish in the later period. Vasopressin also may not participate in blood pressure elevation produced by chronic intracerebroventricular angiotensin II and carbachol, although it plays an important role in acute pressor responses to these agents.

The peripheral renin-angiotensin system does not seem to have a role in the mild hypertension induced by chronic intracerebroventricular NaCl infusion since the depressor response to intravenous captopril administration did not differ between the intracerebroventricular hypertonic NaCl and the isotonic NaCl groups. PRA tended to be low in the hypertonic NaCl group in this study. It is known that acute intracerebroventricular hypertonic NaCl suppresses PRA, and the suppression of PRA was also observed in a chronic study.

Our study demonstrates that chronic intracerebroventricular hypertonic NaCl infusion affects the body fluid homeostasis. There were increased water intake and urinary Na+ excretion, positive water balance, and negative Na+ balance during the time course of intracerebroventricular infusion of 1.5 M NaCl. However, these changes were not so remarkable and might be obscured by the surgical intervention despite our efforts to minimize surgical stress. Decreases in food intake and Na+ excretion were seen in all groups at the beginning of the infusion period. Nonetheless, the changes in water and Na+ balance were consistent with the hyponatremia and low plasma osmolality observed after the 7-day infusion of 1.5 M NaCl. The natriuretic response to intracerebroventricular infusion of hypertonic NaCl could be produced by various factors such as hemodynamic change, vasopressin, and suppression of the renal nerve activity. Suppression of the renin-angiotensin system and release of circulating natriuretic factors might act to reinforce the natriuresis. Precise mechanisms for the natriuresis are not understood completely, but it is reasonable to think that the central nervous system regulates Na+ excretion through those multiple factors in response to sodium overload.

Sodium concentration in CSF was elevated by about 5 meq/l in the rats given intracerebroventricular infusion of 1.5 M NaCl for 7 days. This level is within the physiological range and can be seen after water deprivation, although Na+ concentration in the third ventricular CSF may be somewhat higher than that in the cisternal CSF. It appears that initial increases in water intake, vasopressin release, and natriuresis result in hyponatremia to attenuate the influence of sodium overload on the brain in the chronic phase of intracerebroventricular hypertonic NaCl infusion. Plasma vasopressin was almost normal and did not contribute to the blood pressure elevation in the chronic phase; however, the level of vasopressin was inappropriately low for the raised CSF Na+ concentration and was inappropriately high for the hyponatremia.
The central action of sodium may play an important role in many types of salt-dependent experimental hypertension. In several studies, it was observed that in Dahl salt-sensitive rats and one-kidney, one-clip hypertensive rats, the increase in sodium and vasopressin is stimulated by intracerebroventricular hypertonic saline. Vasopressin might participate in those models of hypertension, although it was not evident in other studies. Because the sympathetic nervous system and vasopressin are stimulated by intracerebroventricular hypertonic NaCl, an increase in sodium intake may activate these systems through the central mechanisms. Furthermore, electrical lesion of the third ventricular area can prevent or attenuate a number of types of experimental hypertension including DOC-salt hypertension, the Dahl salt-sensitive rat, and reduced renal mass hypertension as well as the pressor response to intracerebroventricular hypertonic NaCl infusion in rats.

Our study may provide additional information for understanding the relations among salt, the central nervous system, and hypertension. The hypertension due to chronic intracerebroventricular hypertonic NaCl infusion was mild in this and previous studies. However, it should be mentioned that since the renal function is abnormal and NaCl is given systemically in most forms of salt-dependent hypertension, even the central nervous system may contribute to the pathogenesis. On the other hand, the rats treated with chronic intracerebroventricular hypertonic NaCl infusion had intact kidneys and were out of systemic Na⁺ loading. The intact kidneys, the lack of systemic Na⁺ overload, and the loss of body Na⁺ may restrain the development of profound hypertension. Chronic sodium load on the brain may produce greater increases in blood pressure in the cases of renal dysfunction and systemic sodium load. A report by Soltis and Bohr is consistent with this idea; they observed a significant elevation in blood pressure of rats treated with DOC and chronic intracerebroventricular infusion of 0.6 M NaCl but not in rats given intracerebroventricular infusion of 0.6 M NaCl alone or DOC-treated rats given intracerebroventricular infusion of isotonic NaCl. The interaction between the central nervous system and the kidney in response to sodium overload may be critical in the development and maintenance of salt-induced hypertension.

References


KEY WORDS • sodium chloride • blood pressure • water balance • central nervous system • sympathetic nervous system • catecholamines • vasopressins
Effects of chronic intraventricular sodium on blood pressure and fluid balance.
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