Differential Cardiovascular Effects of Centrally Administered Vasopressin in Conscious Long Evans and Brattleboro Rats

Deborah Harland, Sheila M. Gardiner, and Terence Bennett

The cardiovascular effects of arginine vasopressin (AVP) administered into a lateral cerebral ventricle or into the cisterna magna were investigated in conscious Long Evans (control) rats and AVP-deficient Brattleboro rats. The effects of subpressor intracerebroventricular and intracisternal doses of AVP on cardiac baroreflex sensitivities were also determined. Intracerebroventricular and intracisternal AVP increased blood pressure of both strains of rat in a dose-dependent manner. The maximum pressor response produced by intracerebroventricular AVP in Long Evans rats was 13±2/13±1 mm Hg (systolic/diastolic, n=6) after 100 ng AVP. The pressor response to the highest intracerebroventricular dose of AVP tested in Brattleboro rats (30 ng) was 46±13/21±6 mm Hg (n=6). Intracerebroventricular AVP caused a tachycardia in Brattleboro rats but had no effect on heart rate of Long Evans rats. At doses greater than 1 ng, the increases in blood pressure produced by intracisternal AVP in both groups of rats were significantly greater than the increases produced by the same doses given intracerebroventricularly. Heart rate fell in a dose-dependent manner after intracisternal AVP in Long Evans rats but not in Brattleboro rats. Cardiac baroreflex sensitivities of Brattleboro rats were not significantly different from those of Long Evans rats and were not modified by intracerebroventricular (0.3 ng) or intracisternal (0.1 ng) AVP. In Long Evans rats, intracisternal AVP (0.3 ng) increased cardiac baroreflex responses to both increases and decreases in pressure. Intracerebroventricular AVP (0.3 ng) increased the sensitivity of the reflex in response to an elevation but not to a reduction in blood pressure. These results suggest that Brattleboro rats are more sensitive than Long Evans rats to the central pressor action of AVP and indicate that AVP can modify the baroreflex of Long Evans rats at a site(s) within the brain. Brattleboro rats may maintain normal baroreflex function through mechanisms that do not use, and are not modified by, central AVP. (Circulation Research 1989;65:925–933)

The neurohypophysial hormone arginine vasopressin (AVP) has been localized within a number of extrahypothalamic brain regions, including several nuclei thought to be involved in cardiovascular control. AVP-immunoreactive fibers originating in the paraventricular and supraoptic nuclei project to the locus ceruleus, the nucleus of the solitary tract (NTS), the dorsal vagal complex, and the intermediolateral column of the spinal cord. These are all areas of the central nervous system that may influence sympathetic efferent outflow and/or baroreflex function. In rats, intracerebroventricularly and intrathecally injections of AVP, or microinjection of AVP into specific brain nuclei that include the NTS,10–13 the locus ceruleus,14 and the hypothalamic median preoptic nucleus,15 produce increases in blood pressure and heart rate. The pressor responses following intracerebroventricular administration of AVP to conscious rats were shown to be mediated by increased sympathetic efferent outflow16 and could be inhibited by intracerebroventricular pretreatment with an antagonist of V1 receptors for AVP.17 The concomitant increases in blood pressure, heart rate, and peripheral sympathetic nerve activity produced by intracerebroventricular AVP in conscious rats16 suggest that, in contrast to the effects of circulating AVP, AVP may act at sites within the brain to reduce baroreflex sensitivity.17 In support of this hypothesis, intracerebroventricular administration of a V1-receptor antagonist to conscious rats increased the sensitivity of the baroreflex-mediated fall in heart rate in response to an increase in blood pressure, whereas
intracerebroventricular AVP attenuated baroreflex sensitivity. However, other observations indicated that intracisternal administration of AVP caused a prolonged increase in baroreflex sensitivity of conscious rats, in response to both a rise and a fall in blood pressure. Further conflicting results regarding a possible role for AVP in central cardiovascular regulation have arisen from studies carried out in homozygous Brattleboro rats, which are deficient in hypothalamic and pituitary AVP. Intracerebroventricular administration of high doses of AVP to anesthetized Brattleboro rats produced increases in blood pressure that were not significantly different from those of control rats. In contrast, conscious Brattleboro rats showed significantly smaller increases in blood pressure and heart rate in response to intracerebroventricular AVP than did their genetic controls, that is, Long Evans rats. Imai et al. have reported that Brattleboro rats have markedly suppressed baroreflex sensitivities that can be normalized by an intravenous or an intracerebroventricular infusion of AVP. However, other studies have shown that Brattleboro rats have normal cardiac baroreflex sensitivities compared with Wistar or with Long Evans rats.

The present study was designed to examine more closely the cardiovascular effects of centrally administered AVP in conscious Brattleboro and Long Evans rats. First, we compared the changes in blood pressure and heart rate after administration of AVP into a lateral cerebral ventricle with changes after AVP administration into the cisterna magna; with the latter procedure, AVP is more likely to reach brain stem structures. Second, we investigated the effects of AVP (at doses that had no effect on blood pressure or heart rate) on baroreflex-mediated changes in heart rate after both a rise and a fall in blood pressure. Some of these results have been presented in abstract form to the British Pharmacological Society.

Materials and Methods

All experiments were carried out in male, homozygous Brattleboro rats (343±5 g, 16.5±0.5 weeks old, n=33) and progenitor Long Evans rats (341±5 g, 15±0.5 weeks old, n=35). These animals have been bred in Nottingham since 1980 from stock originally obtained from Charing Cross Hospital Medical School. The rats were anesthetized with methohexital sodium, 60 mg/kg i.p. (Brevital Sodium, Eli Lilly, Indianapolis, Indiana) and positioned in a stereotaxic frame (David Kopf Instruments, from Clark Electromedical Instruments, Pangbourne, UK); the skull was leveled between lambda and bregma. A 23-gauge stainless-steel guide cannula was implanted 1 mm dorsal to the right lateral cerebral ventricle (stereotaxic coordinates, 0.8 mm posterior to bregma, 1.5 mm lateral to the midline, and 3.2 mm ventral to the surface of the skull) or into the cisterna magna. The cannula was secured to the skull with screws and dental cement. Patency of the guide cannula was ensured by inserting a 31-gauge stainless-steel stylet fashioned to extend 0.5 mm beyond the end of the 23-gauge guide. After surgery, the animals were treated with ampicillin trihydrate (Penbritin, Beecham Animal Health, Brentford, UK), 7 mg/kg i.m. At least 7 days later, the animals were reanesthetized briefly with methohexital sodium (60 mg/kg i.p.), and polyethylene catheters filled with heparinized (30 units/ml) 0.9% wt/vol saline were implanted in the abdominal aorta via the caudal artery for recording of blood pressure and in the right jugular vein for intravenous administration of drugs, as described previously. Experiments were begun after an overnight recovery period of 17–18 hours.

Systolic and diastolic blood pressures and heart rates were recorded continuously as previously described with a pressure transducer (type 4-442, Bell & Howell, Wembley, UK) with a modified low volume displacement dome connected, via an amplifier (EMMA, type SE 4001, S.E. Laboratories). In the baroreflex sensitivity experiments, mean arterial pressure, derived by electronically filtering the pulsatile pressure signal, was monitored, together with systolic and diastolic blood pressure and heart rate. Blood pressure and heart rate were allowed to stabilize for at least 30 minutes before beginning the experiments.

Intracerebroventricular and intracisternal injections were made through a 31-gauge stainless-steel injector that extended 1 mm beyond the previously implanted guide cannula. The injector, attached via polyethylene tubing (0.28 mm i.d., 0.61 mm o.d.) to a 20-μl Hamilton microsyringe, was primed with AVP (Cambridge Research Biochemicals, Cambridge, UK) at concentrations between 6 ng/ml and 20 μg/ml of its vehicle (0.9% wt/vol saline) and inserted into the guide cannula without handling the animals. When the animals had resettled, injections of AVP or vehicle were made over a period of 1 minute and in a total volume of 5 μl. Intracerebroventricular and intracisternal injection sites were confirmed in each animal at the end of the experiment by injecting 5 μl of a 1% aqueous solution of Evans Blue dye and examining the brain for staining of the ventricular spaces.

Changes in Blood Pressure and Heart Rate Produced by Intracerebroventricular and Intracisternal AVP

Separate groups of Long Evans and Brattleboro rats received a maximum of three increasing doses of AVP, administered either intracerebroventricularly (Long Evans, 0.3–100 ng; Brattleboro, 0.1–30 ng) or intracisternally (Long Evans, 0.3–30 ng; Brattleboro, 0.03–3 ng). The dose ranges tested were slightly different in the two strains of rat since preliminary experiments revealed that the behav-
ioral effects of intracerebroventricular and intracisternal AVP were observed at lower doses in Brattleboro rats compared with Long Evans rats (see below). The AVP injections were preceded in each animal by an injection of vehicle (0.9% wt/vol saline, 5 μl). Blood pressure and heart rate were monitored for 30 minutes after administration of AVP or vehicle, and the interval between successive injections of AVP was at least 45 minutes.

**Effect of Peripheral \(V_1\) Receptor Blockade on Responses to Intracisternal AVP**

The \(V_1\) AVP antagonist, d(CH2)3Tyr[Et]DAVP, was administered intravenously as a bolus (10 μg/kg in 0.1 ml), followed by continuous infusion of 10 μg/kg/hr (0.3 ml/hr) to a group of six Long Evans rats with indwelling intracisternal canulae. This dose of d(CH2)3Tyr[Et]DAVP was sufficient to abolish completely the pressor response produced by 3 ng AVP administered intravenously. Five minutes after beginning infusion of the AVP antagonist, the animals received an intracisternal injection of vehicle (0.9% wt/vol saline, 5 μl) followed 60 minutes later by an intracisternal injection of AVP (3 ng). Blood pressure and heart rate responses to vehicle or AVP were monitored for 30 minutes after each injection.

**Cardiac Baroreflex Sensitivities**

Increases in blood pressure were evoked by intravenous infusion of methoxamine (0.4 mg/ml, 0.2 ml/min); the infusion was continued until mean arterial pressure had risen by approximately 30 mm Hg. Decreases in blood pressure were evoked by a bolus intravenous injection of sodium nitroprusside (100 μg/ml, 0.1 ml). Slow infusion of methoxamine was used since we have previously shown that cardiac baroreflex responses elicited by bolus injections of pressor agents do not give reliable results, due to the prolonged latency of the pulse interval response to a pressor stimulus in rats. During both the rises and falls in blood pressure, a minimum of eight readings of mean arterial pressure were taken, and the slope of the line relating these values of mean arterial pressure to the pulse interval during the baroreflex tests were obtained by linear regression analysis. In each case, the correlation coefficient was greater than 0.8. Values for baroreflex sensitivities are expressed as median (range) and were compared by the Wilcoxon rank-sum test to avoid making any assumptions about the distribution of the data.

**Results**

**Changes in Blood Pressure and Heart Rate Produced by Intracerebroventricular and Intracisternal AVP**

Intracerebroventricular or intracisternal administration of 5 μl of 0.9% wt/vol saline had no significant effect on blood pressure or heart rate in Long Evans or Brattleboro rats. Intracerebroventricular administration of AVP caused dose-dependent increases in systolic and diastolic blood pressure in both strains (Figure 1, left). Pressor responses produced by intracerebroventricular AVP were maximal approximately 2 minutes after beginning the injections (Figure 2, top). In Long Evans rats, the maximum increase in blood pressure produced by intracerebroventricular administration of AVP was 13±2/13±1 mm Hg (systolic/diastolic, n=6) after a dose of 100 ng (Figure 1, left). Intracerebroventricular administration of AVP had no significant effect on heart rate of Long Evans rats at any dose tested (p>0.05 in each case by analysis of variance). Pressor responses produced by intracerebroventricular AVP in Brattleboro rats were more variable, especially at higher doses, with greater increases in systolic than in diastolic blood pressures (Figure 1, left). At doses of 3 ng and 30 ng, the
changes in systolic, but not in diastolic, blood pressure produced by intracerebroventricular AVP were significantly greater in Brattleboro than in Long Evans rats (Figure 1, left, and Figure 2, top, p<0.05). Pressor responses caused by intracerebroventricular AVP in Brattleboro rats were accompanied by significant increases in heart rate at doses greater than 0.3 ng. This tachycardia was variable and not dose dependent. The maximal changes in heart rate in the first 5 minutes after intracerebroventricular administration of 1 ng, 3 ng, and 30 ng of AVP were 98±17 (n=6), 56±10 (n=7), and 55±19 (n=6) beats/min, respectively. It was not possible to test intracerebroventricular doses higher than 30 ng AVP in Brattleboro rats due to the marked behavioral effects produced by the peptide (i.e., exploratory behavior, rearing, and limb extensions). “Barrel rotations,” which consist of multiple, rapid rotations round the animals’ longitudinal axes were observed in three out of the six animals given the 30-ng dose.

Administration of AVP into the cisterna magna also caused dose-dependent pressor responses in Long Evans and Brattleboro rats (Figure 1, right), which were again maximal about 2 minutes after beginning the injection (Figure 2, bottom). At doses greater than 1 ng, the increases in systolic and diastolic blood pressure produced by intracisternal AVP in both groups of rats were significantly greater than the increases produced by the same doses given intracerebroventricularly (p<0.05 in each case, Figures 1 and 2). This was most evident for Long Evans rats, as the dose-response curve for the pressor effect of intracisternal AVP (Figure 1, right) was much steeper than the dose-response curve to intracerebroventricular AVP in these animals (Figure 1, left). At doses above 0.3 ng, Brattleboro rats were more sensitive than Long Evans rats to the pressor actions of AVP administered intracisternally (Figure 1, right, and Figure 2, bottom). AVP administered intracisternally had contrasting effects on the heart rate of Long Evans and Brattleboro rats. In Long Evans rats, doses of 3 ng and 30 ng produced a significant bradycardia (~55±24 beats/min and ~77±11 beats/min, respectively, p<0.05 in each case, n=6). In Brattleboro rats, only the highest dose of AVP tested intracisternally (3 ng) had a significant effect on heart rate, producing a tachycardia (50±19 beats/min, n=6) at the time of the peak pressor response (Figure 2, bottom). Behavioral effects of AVP again prevented the construction of a full dose-response curve. The highest dose tested in Long Evans rats was 30 ng, and in Brattleboro rats it was 10-fold lower (i.e., 3 ng).

Effect of Peripheral V1-Receptor Blockade on Responses to Intracisternal AVP

The antagonist of the V1-mediated vasoconstrictor effects of AVP, d(CH2)5Tyr[Et]DAVP, administered intravenously had no significant effect on blood pressure or heart rate of Long Evans rats. Blood pressure was 138±2/79±1 mm Hg (n=6) immediately before administration of d(CH2)5Tyr[Et]DAVP and 135±3/76±2 mm Hg 5 minutes later. Corresponding values of heart rate were 357±18 beats/min and 366±16 beats/min. Pretreatment with the AVP antagonist had no significant effect on the increase in blood pressure and decrease in heart rate produced by 3 ng AVP administered intracisternally to Long Evans rats (Figure 3).

Cardiac Baroreflex Sensitivities

Resting levels of blood pressure and heart rate were not significantly different in the four groups of animals in this part of the study (Table 1). Intravenous infusion of methoxamine increased mean arterial pressure by 41±2 mm Hg (n=17, mean of all control responses) in Long Evans rats and by 42±2 mm Hg (n=16) in Brattleboro rats. Sodium nitroprusside caused a decrease in mean arterial pressure
of 38±2 mm Hg (n=16) and 36±2 mm Hg (n=16) in Long Evans and Brattleboro rats, respectively. The control cardiac baroreflex sensitivities of Brattleboro rats in response to both a rise and fall in blood pressure were not significantly different from those of Long Evans rats and were not modified by subpressor intracerebroventricular or intracisternal doses of AVP (Table 2). In Long Evans rats, a subpressor intracisternal dose of AVP (0.3 ng) increased the sensitivity of the cardiac baroreflex response to both an increase and a decrease in blood pressure (Table 2). Intracerebroventricular AVP (0.3 ng) increased the sensitivity of the reflex in response to methoxamine but had no significant effect on the response to sodium nitroprusside (Table 2).

Discussion

The results of the present study show that intracerebroventricular and intracisternal administration of AVP caused dose-dependent increases in blood pressure of Long Evans and Brattleboro rats; the latter were more sensitive than the former. In addition, the pressor effects were greater in both strains of rat when AVP was administered intracisternally than when it was administered intracerebroventricularly.

The observation that Brattleboro rats were more sensitive than Long Evans rats to the pressor effects of centrally administered AVP is not consistent with results from a previous study in which the increases in blood pressure and heart rate produced by intracerebroventricular AVP were significantly less in Brattleboro rats than in Long Evans rats and considerably less than the pressor effects of intracerebroventricular AVP in the Brattleboro rats used in the present study. However, in that study animals were conscious, but restrained; this may explain why full dose-response curves were obtained using doses of AVP (100 ng and above) that would have caused motor disturbances in both the Long Evans and Brattleboro rats in our study. One other difference between the two studies, which may account for the inconsistent results, is the source of Brattleboro rats used in the experiments. If breeding source and breeding practices do have an important influence on the responses to centrally admin-

FIGURE 2. Graphs showing blood pressure and heart rate of Long Evans and Brattleboro rats before and after intracerebroventricular (I.C.V., top) or intracisternal (I.C., bottom) administration of 3 ng arginine vasopressin (AVP) (t=0 min). Each point is the mean±SEM.

FIGURE 3. Graphs showing maximum changes in systolic (SBP) and diastolic (DBP) blood pressure and heart rate produced by 3 ng intracisternal (ic) arginine vasopressin (AVP) or 5 µl vehicle (0.9% w/vol saline) in control Long Evans rats and in a group of Long Evans rats pretreated with the V1 vasopressin antagonist, d(CH2)5Tyr[Et]DAVP. Vertical lines represent the standard error of the mean, n=6.
istered AVP in these animals, it would then seem unlikely that the differences observed between Brattleboro and control Long Evans rats are due primarily to an absence of endogenous AVP. Interestingly, it has been shown that Brattleboro rats are more sensitive than Long Evans rats to the motor effects of repeated central administration of high doses of AVP34 and that these effects of AVP appear to be receptor-mediated.35 Those results suggest a fundamental difference in receptor-mediated responses to AVP in Brattleboro rats and are more consistent with our present findings of a greater pressor sensitivity to centrally administered AVP in these animals.

Our present findings suggest that, although Brattleboro rats are deficient in hypothalamic AVP, they have functional receptors for the peptide.34 These observations are consistent with the identification of AVP binding sites in the pituitary and septum of Brattleboro rats.36-37 Although significantly greater numbers of AVP binding sites have been observed in septum membrane preparations from homozygous Brattleboro rats compared with heterozygous controls, the affinity of AVP for these binding sites was reduced. In addition, similar numbers of AVP binding sites were present in renal medullary membranes from the two strains.37 These data suggest that some degree of up-regulation of AVP receptors, at least in the central nervous system, may occur in the absence of endogenous AVP. Radioligand binding data do not indicate, however, any concomitant changes in receptor-effector coupling that would determine the functional responses to AVP receptor activation. Up-regulation of AVP receptors would be consistent with an enhanced pressor response to AVP in Brattleboro rats (this study) rather than the diminished pressor response reported by other workers.20 It is unlikely that Brattleboro rats are generally supersensitive to centrally administered pressor peptides since responses to intracerebroventricular angiotensin II38 and to neuropeptide Y administered into the third ventricle39 were reduced in Brattleboro compared with Long Evans rats.

The results of the present study do not permit precise localization of the AVP-mediated changes in blood pressure and heart rate. However, since both intracisternal and intracerebroventricular AVP produced increases in blood pressure and these responses were significantly greater when AVP was administered intracisternally than when the same doses were given intracerebroventricularly, it is feasible that AVP acts at the same site when administered by these two routes. The smaller increases in blood pressure following intracerebroventricular AVP may reflect diffusion of the peptide to this site

<table>
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<th>Group</th>
<th>n</th>
<th>Systolic (mm Hg)</th>
<th>Diastolic (mm Hg)</th>
<th>Mean (mm Hg)</th>
<th>Heart rate (beats/min)</th>
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<td>Long Evans</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>ICV</td>
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<td>88±2</td>
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<tr>
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<tr>
<td>IC</td>
<td>8</td>
<td>147±4</td>
<td>87±3</td>
<td>108±3</td>
<td>360±11</td>
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</tbody>
</table>

Results are expressed as mean±SEM. ICV, intracerebroventricular; IC, intracisternal.

Table 2. Effect of Intracerebroventricular and Intracisternal Arginine Vasopressin on Cardiac Baroreflex Sensitivities of Long Evans and Brattleboro Rats

<table>
<thead>
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<th>Group</th>
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<th>Nitroprusside</th>
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</tr>
<tr>
<td>Control</td>
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<td>1.22 (0.75–1.53)</td>
<td>0.72 (0.40–1.60)</td>
</tr>
<tr>
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<td>0.75 (0.45–1.45)</td>
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<tr>
<td>Control</td>
<td></td>
<td>1.19 (0.88–1.56)</td>
<td>0.73 (0.40–1.29)</td>
</tr>
<tr>
<td>IC AVP (0.3 ng)</td>
<td>8</td>
<td>1.55 (0.96–2.40)*</td>
<td>1.55 (0.40–2.34)*</td>
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<tr>
<td>Brattleboro</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Control</td>
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<td>0.90 (0.63–1.54)</td>
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<td>Control</td>
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<td>0.73 (0.40–1.60)</td>
<td>0.96 (0.54–2.67)</td>
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Results are expressed as median value; numbers in parentheses represent the range. ICV, intracerebroventricular; AVP, arginine vasopressin; IC, intracisternal. *p<0.05 compared with respective control (Wilcoxon test).
of action (possibly the hindbrain) and hence a reduced effective concentration at that site. However, there was no difference between the time taken for AVP to cause a maximal change in blood pressure when it was given intracerebroventricularly or intracisternally (see Figure 2). In addition, AVP administered by each route had different effects on heart rate. For example, intracisternal AVP caused a bradycardia in Long Evans rats, whereas intracerebroventricular AVP had no significant effect on heart rate. These results suggest, therefore, that intracisternal and intracerebroventricular AVP may act at different sites in the brain to produce these cardiovascular effects. Studies by other workers have shown that pretreatment with a V₁ receptor antagonist prevents the cardiovascular effects of subsequent intracerebroventricular injections of AVP; this finding suggests that these effects are mediated through stimulation of V₁ receptors accessible from the cerebrospinal fluid.16,17

Intracisternal injections of AVP would be expected to reach brain stem structures more readily than intracerebroventricular injections; the latter should reach forebrain as well as hindbrain areas. AVP binding sites have been identified in the NTS, 40-42 ventrolateral medulla, 40,41 and spinal cord,9 which are all possible sites of action for AVP administered intracisternally. In particular, microinjection of AVP into the NTS has been reported to produce increases in blood pressure in anesthetized Brattleboro and control rats.10-12-13 It is possible that the differential heart rate changes induced by intracerebroventricular and intracisternal administration of AVP in Long Evans and Brattleboro rats may reflect a difference in baroreflex buffering of the pressor changes induced by AVP in the two strains. The area postrema, which is anatomically close to the NTS and is outside the blood-brain barrier, has been implicated as a possible site for the modulatory actions of circulating AVP on baroreflex sensitivity.43,44 It has been suggested that such a modulatory action may involve stimulation of V₂ rather than V₁ receptors (see also below).16,17

The failure of intravenous administration of the V₁-receptor antagonist d(CH₂)₅Tyr[Et]DAVP to modify the pressor and bradycardic effects of intracisternal AVP in our Long Evans rats suggests that these effects were not due to leakage of the peptide into the periphery.

The finding that Brattleboro rats have normal cardiac baroreflex sensitivities is not consistent with previous reports of much reduced baroreflex sensitivity after a pressor stimulus in these animals21,22 but is consistent with earlier work from our laboratory that indicated only modest differences between cardiac baroreflex sensitivities of Long Evans and Brattleboro rats.23 Imai et al21,22 also reported that intravenous or intracerebroventricular infusion of low doses of AVP (2 ng/kg/min) restored baroreflex sensitivity of Brattleboro rats to within the normal range, but they did not test the effects of AVP in Long Evans rats. Since Brattleboro rats are more sensitive than Long Evans rats to the central pressor effects of AVP (this study) and therefore appear to possess functional AVP receptors, it is at first sight surprising that we found subpressor intracerebroventricular and intracisternal doses of AVP increased baroreflex sensitivity of Long Evans rats but were without effect in Brattleboro rats. Other workers have reported that intracerebroventricular administration of a V₁-receptor antagonist had no effect on baroreflex sensitivity of Brattleboro rats.17 It is possible, therefore, that Brattleboro rats maintain normal baroreflex function through mechanisms that do not use and are not modified by AVP (see also below).

In Wistar rats, intracisternal AVP has been reported to produce prolonged sensitization of baroreflex-mediated heart rate responses to both a rise and a fall in blood pressure.18 However, the dose of AVP used in that study (10 ng) was 30-fold higher than the dose we have used to demonstrate the effects of AVP on baroreflex sensitivity of Long Evans rats and would certainly have caused significant changes in blood pressure and heart rate in our hands.

Both the results of the present study and those of Petty et al18 are not consistent with the demonstration that intracerebroventricular AVP decreased the sensitivity of the baroreflex-mediated fall in heart rate in response to a pressor stimulus in conscious Wistar rats, whereas intracerebroventricular administration of a V₁ AVP antagonist increased baroreflex sensitivity.17 An attenuation of the baroreceptor reflex by AVP within the brain is consistent with its centrally mediated pressor effect, whereas an enhancement of baroreflex sensitivity appears contradictory to these effects. The results of Unger et al17 suggest that AVP attenuates baroreflex sensitivity via an action on V₁ receptors accessible from the cerebrospinal fluid. It is not known whether the central cardiovascular effects of AVP are altered by pretreatment with V₁-receptor antagonists since the currently available compounds are too neurotoxic to test in conscious animals.19 However, intravenous administration of a V₂ antagonist decreased baroreflex sensitivity of control rats both when renal volume losses were replaced and when they were not; this finding suggests that circulating AVP may influence the baroreceptor reflex through stimulation of V₂ rather than V₁ receptors.17 Interestingly, this may not be the case in Brattleboro rats since intravenous administration of a V₂ antagonist failed to modify baroreflex sensitivity in this strain. This may be consistent with the variable heart rate changes we observed after intracisternal administration of AVP to Long Evans and Brattleboro rats.

In conclusion, the results of the present study suggest that AVP-deficient Brattleboro rats are more sensitive than control Long Evans rats to the central pressor and behavioral actions of AVP.
more, AVP may exert differential effects on the cardiovascular system of conscious rats depending on the site of injection into the cerebrospinal fluid. Although suprressor doses of AVP sensitized the baroreceptor reflex of Long Evans rats (suggesting that AVP can modify the baroreflex at a site(s) within the brain), Brattleboro rats had normal cardiac baroreflex sensitivities that were unaffected by intracerebroventricular or intracisternal AVP. Clearly, further studies are required to elucidate, fully, the role of AVP in central cardiovascular control.

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**Key Words** • vasopressin • blood pressure • baroreceptor reflex • central nervous system • Brattleboro rat
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