Preoptic recess noradrenergic receptors control modification of baroreflex sensitivity by hypertonicity

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Bealer, Steven L. Preoptic recess noradrenergic receptors control modification of baroreflex sensitivity by hypertonicity. Am. J. Physiol. 276 (Regulatory Integrative Comp. Physiol. 45): R44–R51, 1999.—These studies examined the effects of α1- and α2-adrenoceptor blockade in the anteroventral portion of the third cerebral ventricle (AV3V) on modification of baroreflex-induced changes in heart rate and renal sympathetic nerve activity (RSNA) induced by hyperosmolality. Local administration of hypertonic artificial cerebrospinal fluid (aCSF) in the AV3V significantly increased baroreflex-induced bradycardia during intravenous phenylephrine but did not alter changes in RSNA during the pressor response or alter tachycardia and neural responses evoked by decreased blood pressure. The enhanced cardiac response was not observed during simultaneous administration of phenolamine (α1- and α2-antagonist) or yohimbine (selective α2-antagonist) in the AV3V region. However, treatment with prazosin (α1-antagonist) did not alter the exaggerated cardiac response evoked by hypertonic aCSF to increased blood pressure. These data demonstrate that acute, local hypertonic stimulation in the AV3V region selectively enhances baroreflex-induced bradycardia by stimulation of α2-adrenoceptors during acute pressor responses.

norepinephrine; anteroventral third ventricle; sympathetic nerve activity; bradycardia; baroreceptor

DIRECT ADMINISTRATION of hypertonic solutions into the central nervous system (CNS) alters baroreflex sensitivity. For example, lateral ventricular injection of 1.0 M NaCl solution decreases the gain and range of cardiac responses when blood pressure is increased 60 min after central hypertonic saline treatment (28). In addition, other studies have shown that chronic (11 days) infusion of hypertonic saline into the third cerebral ventricle increases blood pressure without a concomitant inhibition of sympathetic nerve activity (24). Furthermore, direct tests of baroreflex sensitivity found that baroreflex-induced changes in heart rate were diminished after long-term central infusion of hypertonic saline, whereas responses in renal sympathetic nerve activity (RSNA) were unaltered (10).

The specific sites and neurotransmitter systems within the CNS that control modification of baroreflex sensitivity induced by central administration of hypertonic solutions have not been determined. However, several findings suggest that noradrenergic mechanisms in the periventricular tissue surrounding the anteroventral portion of the third cerebral ventricle (AV3V) may participate in this response. For example, infusion of hypertonic saline into the third ventricle increases blood pressure (9, 10), and electrolytic ablation of this brain region attenuates or abolishes several behavioral and physiological responses evoked by peripheral and CNS administration of hypertonic solutions (8, 19). Furthermore, local blockade of α1- and α2-adrenoceptors in the AV3V region prevents blood pressure and/or heart rate responses induced by intravenous infusion of hypertonic saline (5).

Taken together, these data support the hypothesis that noradrenergic receptors in the AV3V region contribute to the cardiovascular responses induced by either central or systemic hyperosmotic stimulation. However, the role of these receptors in changes in baroreflex sensitivity produced by central administration of hypertonic solutions has not been directly tested. Determining the role of noradrenergic receptors in this brain region will expand our understanding of the AV3V area as an integrative center controlling autonomic responses to hyperosmolality. Furthermore, results from these experiments will define this brain region as part of a central circuit that may contribute to altered baroreflex sensitivity. Delineating CNS sites and neurotransmitters that control the magnitude of baroreflex-induced responses will suggest potential mechanisms that could account for overriding of the baroreflex during periods when both increased blood pressure and heart rate are desirable, as well as decreased baroreflex sensitivity observed during experimental treatments such as altered sodium diet (16, 17) and sodium-dependent hypertension (13, 30). Therefore, these studies were designed to evaluate the effects of local administration of a hypertonic stimulus in the AV3V region on baroreflex-induced changes in heart rate and sympathetic nerve activity and determine whether stimulation of AV3V adrenergceptors contributes to altered baroreflex sensitivity.

Local administration of hypertonic stimuli to the AV3V region was used to eliminate the confounding effects produced by stimulation of peripheral osmoreceptors, and/or concomitant stimulation of osmotically sensitive neurons located in other regions of the CNS, produced by either intravenous or lateral cerebroventricular administration of hyperosmotic solutions. Defining a specific brain site modulating baroreflex sensitivity will provide an anatomic locus for subsequent studies evaluating cellular and molecular mechanisms that mediate baroreflex-induced cardiac responses.

METHODS

Animals. Male Sprague-Dawley rats (Harlan) were housed in hanging wire cages in a room maintained on a 12:12-h light-dark cycle with ad libitum access to food and water. Animals weighed between 250 and 310 g at the time of testing.

Surgery. On the day before the experiment, rats were anesthetized with methohexital sodium (Brevital; 60 mg/kg) and placed in a stereotaxic instrument. The scalp was incised and retracted laterally to allow a 2-mm hole, centered on
bregma, to be drilled through the skull. A loop-style microdialysis probe (3, 25) was placed so that the tip was in the ventral portion of the anterior canal of the third ventricle, adjacent to the lamina terminals (0.2 mm posterior to bregma, 0.0 mm lateral to the midline, and −7.9 mm ventral to the skull). The dialysis probe was secured to the skull with small screws and dental acrylic, and animals were returned to their home cages.

On the day of testing, animals were again anesthetized with Brevital (60 mg/kg) and implanted with two catheters (PE-10 cemented into PE-50 polyethylene tubing) in a femoral vein and a catheter in a femoral artery. All catheters contained heparin saline (50 U heparin/ml saline).

Sympathetic nerve activity was recorded from a branch of the left renal nerve. After a retroperitoneal incision was made and the kidney exposed, a nerve bundle entering the kidney was isolated and cleared of fat and connective tissue for a length of 5–10 mm. The nerve was then placed on bipolar platinum wire electrodes. After an optimal nerve recording was obtained, the distal portion of the nerve was crushed and the nerve and electrodes were encased in silicone rubber (Wacker Sil-Gel, 604). Nerve activity was continuously monitored with an audio monitor and oscilloscope and was amplified (Grass PS111 Amplifier), rectified, and integrated (Grass 7P3 Rectifier/Integrator). Supplemental Brevital was administered intravenously as needed during preparation of the renal nerve.

After the catheters were implanted and the nerve was prepared for recording, no additional Brevital was given. Animals were administered a bolus injection of chloralose (40 mg/kg iv), followed by a continuous chloralose infusion (20–40 mg·kg⁻¹·h⁻¹ in 200–400 µl/h) from a syringe placed in a pump and attached to one venous catheter with polyethylene tubing. The chloralose (25 mg/ml) was dissolved in Na₂B₄O₇ (50 mg/ml) (7, 15, 20, 27). Testing did not begin for 60–90 min after the cessation of Brevital.

Cardiovascular and nerve activity recording. Blood pressure was monitored from the arterial catheter using a pressure transducer and MacLab/4e data acquisition system. Heart rate was calculated from the arterial pressure pulses by an internal rate meter in the MacLab. Blood pressure, heart rate, and the rectified, integrated RSNA were recorded by the MacLab data acquisition system and stored on a Power Macintosh 7200 computer.

Baroreceptor reflex responses. Baroreflex responses were evaluated by measuring the relationship between changes in mean arterial blood pressure and changes in heart rate and RSNA during acute pressor and depressor responses. Blood pressure was increased with intravenous infusion of phenylephrine (5–20 µg·kg⁻¹·min⁻¹) and decreased by intravenous infusion of nitroprusside (5–20 µg·kg⁻¹·min⁻¹). These vasoactive agents were administered in random order, and the infusion rate was adjusted so that a ramp change in blood pressure was obtained during a 60- to 90-s period. Sequential infusions were separated by at least 30 min.

Protocol. During the 60- to 90-min equilibration period, dialysis probes were perfused with normal artificial cerebrospinal fluid (aCSF; in mM: 126.5 NaCl, 4 KCl, 1.5 KH₂PO₄, 11 CaCl₂, 2.5 dextrose, 0.83 MgCl₂, 0.5 NaSO₄, 295 mosmol/kgH₂O). Control (Con) baroreflex responses were then obtained with intravenous phenylephrine and nitroprusside infusions. In some animals, dialysis probe perfusion with normal aCSF was continued, whereas in other animals dialysis was changed to a hypertonic aCSF (HT aCSF) containing 160 mM NaCl and having osmolality of 315 mosmol/kgH₂O. Baroreflex response curves were repeated following a 30-min perfusion with HT aCSF (Exp). Dialysis probes in other animals were perfused with normal aCSF during the Con period and with HT aCSF containing either phenylephrine (α₁₇, α₁₂-antagonist, 3.15 × 10⁻³ M), yohimbine (α₁₂-antagonist, 2.3 × 10⁻⁴ M), or prazosin (α₁-antagonist, 2.5 × 10⁻⁴ M) during the Exp period. These doses were selected because they are effective in abolishing changes in blood pressure and/or heart rate to intravenous hypertonic saline (5), as well as other physiological responses (6, 26), when administered locally in the CNS through similarly constructed microdialysis probes.

These studies demonstrated that yohimbine was the most effective adrenergic antagonist in eliminating the enhanced cardiac response evoked by hyperosmotic stimulation of the AV3V region. To ensure that the effects of α₁₂-adrenergic blockade on baroreflex sensitivity were specific for hyperosmolarity, baroreflex-induced responses were tested in a separate group of animals during dialysis probe perfusion with normal aCSF during the Con period and with normal aCSF containing yohimbine during the Exp period.

Nonbiological background noise was determined at the end of each experiment by measuring the amount of electrical activity present in the renal nerve after intravenous administration of hexamethonium (25 mg/kg) in most animals. Other rats were killed, and RSNA was recorded for 45 additional minutes to determine background noise. These measures were equivalent, and the obtained values were subtracted from nerve activity present during the experiment.

Histology. After testing, animals treated with hexamethonium to obtain nonbiological electrical activity were anesthetized with pentobarbital sodium (Nembutal, 60 mg/kg) and transcardially perfused with saline and saline-Formalin solution. Brains from animals used to measure postmortem nerve activity were removed from the skull without perfusion and placed in Formalin. All brains were stored in Formalin containing sucrose (30%) and subsequently frozen, cut in 40-µm sections, and stained with cresyl violet. The sections containing the AV3V region were observed under the light microscope to determine placement of the microdialysis probe tip.

Data analysis and statistics. Mean changes in blood pressure, heart rate, and RSNA (as percent control) were calculated for sequential 5-s intervals during the infusions of phenylephrine and nitroprusside. Linear regression analyses were performed to determine the blood pressure-heart rate and blood pressure-RSNA relationships. The slopes of the regression lines relating change in blood pressure to change in heart rate or change in RSNA during increased and decreased blood pressure were used as estimates of baroreflex sensitivity. Responses during pressor and depressor responses were analyzed separately.

A two-way analysis of variance with repeated measures was used to compare control values of blood pressure, heart rate, and RSNA, as well as the slopes of the blood pressure-heart rate and blood pressure-RSNA relationships during the Con and Exp periods for all experimental groups. A Newman-Keuls a posteriori test was used to evaluate differences between individual means. A significance level of P < 0.05 was considered significant.

RESULTS

In all animals, dialysis probes were placed in the anterior canal of the third cerebral ventricle. The dialysis membrane was located just posterior to the lamina terminalis and extended from the floor of the third ventricle to the level of the ventral median preoptic nucleus. No animal used in the data analysis
sustained damage to the tissues of the lamina termina-

Table 1 shows basal values for blood pressure, heart rate, and RSNA for all experimental groups during the Con period and after 30-min perfusion with the experimental dialysate. There were no significant differences between groups in these variables during the Con period. Perfusion of dialysis probes with HT aCSF alone, with normal aCSF containing yohimbine, or with HT aCSF containing adrenergic blocking agents did not significantly alter blood pressure or RSNA in any experimental group (Table 1). Furthermore, HT aCSF alone, normal aCSF containing yohimbine, or HT aCSF containing phentolamine or yohimbine did not change resting heart rate. However, HT aCSF containing prazosin produced a significant tachycardia. In addition, there were no significant differences between groups in the slopes of baroreflex-induced changes in heart rate or RSNA obtained during the Con periods.

Changes in heart rate and RSNA were compared with changes in blood pressure of $-36 \pm 1$ mmHg during nitroprusside infusion and $45 \pm 1$ mmHg during phenylephrine infusion. The relationships between blood pressure and heart rate and blood pressure and RSNA were linear through these ranges, and all correlation coefficients were statistically significant ($P < 0.01$).

Figure 1 shows the mean slopes of the baroreflex functions obtained from animals perfused with normal aCSF during the Con and Exp periods ($n = 7$). There were no differences in baroreflex sensitivity of heart rate or RSNA during sequential baroreflex tests when normal aCSF was perfused through the dialysis probes. However, perfusion of HT aCSF during the Exp ($n = 8$) period resulted in a significant increase in the slope of the regression lines relating bradycardia to the increased blood pressure produced by intravenous phenylephrine (Fig. 2). In contrast, the sensitivity of baroreflex-induced changes in RSNA during hypertension were not altered by local administration of HT aCSF into the AV3V region. Although the heart rate response to decreased blood pressure during HT aCSF perfusion tended to be reduced, this difference was not statistically significant. Finally, HT aCSF did not alter baroreflex-induced responses in RSNA during the depressor response.

Figure 3 illustrates the slopes of baroreflex responses when microdialysis probes were perfused with normal aCSF and subsequently with HT aCSF containing phentolamine ($n = 7$). Baroreflex sensitivity of heart rate during increased blood pressure when dialysis probes were perfused with HT aCSF containing phentolamine was not different from that observed during dialysis probe perfusion with normal aCSF. In addition, there were no differences in the baroreflex-induced responses during intravenous nitroprusside or in RSNA in response to either phenylephrine or nitroprusside.

Administration of selective $\alpha$-adrenergic antagonists showed that the increase in cardiac baroreflex sensitivity induced by AV3V perfusion with HT aCSF during

<table>
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<tr>
<th>Group (Exp Dialysate)</th>
<th>Control Period</th>
<th>Experimental Period</th>
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<tr>
<td></td>
<td>MAP, mmHg</td>
<td>HR, beats/min</td>
</tr>
<tr>
<td>aCSF</td>
<td>111 ± 4</td>
<td>372 ± 9</td>
</tr>
<tr>
<td>HT aCSF</td>
<td>105 ± 6</td>
<td>380 ± 14</td>
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<tr>
<td>HT aCSF + Phen</td>
<td>115 ± 5</td>
<td>378 ± 10</td>
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<tr>
<td>HT aCSF + Yoh</td>
<td>111 ± 3</td>
<td>383 ± 15</td>
</tr>
<tr>
<td>HT aCSF + Pra</td>
<td>116 ± 5</td>
<td>385 ± 18</td>
</tr>
<tr>
<td>aCSF + Yoh</td>
<td>115 ± 6</td>
<td>382 ± 12</td>
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Values are means ± SE. Control period, during perfusion with normal artificial cerebrospinal fluid (aCSF). Experimental period, during perfusion with experimental (Exp) dialysate. MAP, mean arterial pressure; HR, heart rate; RSNA, renal sympathetic nerve activity; HT, hypertonic; Phe, phentolamine; Yoh, yohimbine; Pra, prazosin. *$P < 0.05$ relative to control period.
pressor responses is mediated by stimulation of \( \alpha_2 \)-adrenergic receptors. Dialysis probe perfusion with HT aCSF containing yohimbine \((n = 8)\) during the Exp period abolished the enhanced bradycardia evoked by increased blood pressure (Fig. 4). However, yohimbine did not alter the fall in heart rate to intravenous phenylephrine during dialysis probe perfusion with normal aCSF \((n = 7)\). Finally, perfusion of the AV3V with HT aCSF containing prazosin \((n = 7)\) did not prevent the increased bradycardic response during intravenous phenylephrine (Fig. 6).

There were no significant within- or between-group differences in baroreflex-induced changes in RSNA. Furthermore, heart rate responses during nitroprusside infusion were similar in all groups of animals during Con and Exp periods. Table 2 shows the results of both between- and within-group comparisons of slopes of the regression lines relating changes in blood pressure to changes in heart rate during intravenous phenylephrine. Perfusion of the AV3V region with HT aCSF significantly increased baroreflex sensitivity compared with the Con condition and compared with animals perfused with normal aCSF during the Exp period.

When the HT aCSF contained phentolamine, baroreflex sensitivity during the Exp period was not significantly different from the Con condition or from animals perfused with normal aCSF during the Exp period. Similarly, baroreflex sensitivity during perfusion with dialysate containing HT aCSF and yohimbine was not significantly different from the Con period or from animals perfused with normal aCSF during the Exp period. Furthermore, baroreflex sensitivity during perfusion with HT aCSF and yohimbine was significantly lower than that observed in animals perfused with HT aCSF alone during the Exp period. However, yohimbine did not alter heart rate responses to intravenous phenylephrine during AV3V perfusion with normal aCSF. Finally, perfusion with HT aCSF and prazosin did not reduce the increase in baroreflex-induced bradycardia induced by HT aCSF.

**DISCUSSION**

These experiments demonstrate that local administration of HT aCSF in the AV3V region significantly increases sensitivity of the cardiac component of the baroreflex response during increases in blood pressure induced by intravenous phenylephrine. However, changes in RSNA were not altered by HT aCSF administration in the AV3V area, and baroreflex-induced responses evoked by hypotension were not changed by hypertonic stimulation of the AV3V area. Furthermore, the enhanced baroreflex sensitivity produced by HT aCSF during phenylephrine-induced pressor responses is mediated by stimulation of \( \alpha_2 \)-adrenergic receptors located in the AV3V region.

The periventricular tissue surrounding the AV3V is critical for several responses evoked by central hyperos-
molality, including increased blood pressure, thirst, and vasopressin release (8, 19). More recent work has suggested that α₂-adrenoreceptors in this brain region are critical in regulating pressor responses (5), bradycardia (5), and increased atrial natriuretic peptide release (2) during systemic hyperosmotic stimulation. The present results extend these findings by reporting that changes in sensitivity of the cardiac component of the baroreflex evoked by local hypertonicity in the AV3V region are similarly regulated by α₂-adrenergic receptor stimulation in this brain area.

Previous reports have demonstrated the importance of central α₂-adrenergic receptors in regulating normal baroreflex sensitivity. For example, blockade of α₂-adrenergic receptors following vertebral artery administration of yohimbine decreased baroreflex-induced bradycardia, whereas an α₂-receptor agonist increased the fall in heart rate during carotid nerve stimulation (18). In addition, excitation of α₂-adrenergic receptors in the area postrema is necessary for the enhanced baroreflex-mediated inhibition of RSNA and bradycardia induced by vasopressin (14). These data are consistent with the hypothesis that central α₂-adrenergic receptor stimulation at specific brain sites enhances baroreflex-evoked responses during acute increases in blood pressure. The present study demonstrates that the AV3V periventricular tissue contains α₂-adrenergic receptors that potentiate baroreflex sensitivity of cardiac responses when stimulated with hypertonicity.

Although these studies show that AV3V α₂-adrenergic receptors can modify baroreflex sensitivity of heart rate during local hyperosmolality, there is no evidence that the AV3V region participates in normal baroreflex responses. Indeed, electrolytic ablation of AV3V periventricular tissue does not alter cardiac function during intravenous phenylephrine or nitroprusside (4), demonstrating that neural tissue in this brain region is not contributing to normal baroreflex sensitivity. Taken together, these data suggest that although noradrenergic neurons in the AV3V region do not contribute to normal baroreflex responses, these receptors appear critical for modification of baroreflex sensitivity during central hyperosmolality.

Previous experiments that administered hypertonic solutions into the CNS report decreased cardiac baroreflex sensitivity during increased blood pressure. For example, chronic perfusion of the third ventricle with 0.8 M hypertonic saline for 2 or 11 days selectively decreases bradycardia during intravenous phenylephrine while not altering sympathetic nerve responses or affecting either heart rate or nerve activity in response to hypotension in chloralose-anesthetized rats (10). In addition, lateral ventricular injections of 100 µl of 1 M NaCl 1 h before testing also reduced heart rate responses during pressor responses in conscious animals (28). However, in the present study bradycardic responses to intravenous phenylephrine were enhanced by HT aCSF. This discrepancy may be due to the
large concentrations of sodium, 2) longer perfusion times, or 3) peripheral and/or whole brain administration of hypertonic solutions characteristic of previous experiments. The present studies used aCSF containing 160 mM sodium applied locally to the AV3V region for 30 min before examining baroreflex sensitivity. It is possible that longer stimulation times with more concentrated solutions resulted in the previously observed decrease in cardiac baroreflex sensitivity. Similar qualitative changes in baroreflex sensitivity over the course of continuous intravenous infusions of angiotensin II have been demonstrated (21, 22).

Although chloralose anesthesia can diminish the magnitude of baroreflex-induced heart rate responses (23), it has not been shown to produce qualitatively opposite responses compared with those obtained in conscious animals. Furthermore, it is unlikely that anesthesia contributed to the dissimilar responses found in these studies and previous reports, because the earlier investigation perfusing hypertonic saline into the third ventricle also tested baroreflex sensitivity in chloralose-anesthetized animals (10).

The composition of HT aCSF in these studies was selected because the increase in osmolality of aCSF containing 160 mM NaCl approximates the increase in plasma osmolality (20 mosmol/kgH2O) observed during the acute peripheral infusion of hypertonic saline used in previous experiments (1, 5). However, although this increase in plasma osmolality produces hypertension and bradycardia (1, 5), local administration of HT aCSF in the AV3V region did not change blood pressure or heart rate. These differences could be due to peripheral effects of hypertonic saline and/or simultaneous osmotic stimulation of other brain areas resulting from intravenous infusions. Alternatively, it is not possible to determine the precise osmolality at the critical neurons in the AV3V region during dialysis probe perfusion with HT aCSF. Therefore, the osmotic stimulus at this site may not have been equivalent to that produced during intravenous hypertonic infusion, which raised plasma osmolality 20 mosmol/kgH2O. Regardless, because blood pressure did not change during AV3V administration of HT aCSF, the enhanced cardiac baroreflex sensitivity cannot be attributed to a concomitant pressor response. This is consistent with an earlier report demonstrating altered heart rate responses occur before increased blood pressure during third ventricular infusion of hypertonic saline (10).

The effect of $\alpha_1$-adrenergic blockade on heart rate is consistent with previously published findings on the role of AV3V $\alpha_2$-adrenergic receptors in cardiac function. Local injections of norepinephrine into the median preoptic nucleus, located in AV3V tissue, induce bradycardia (12), and prazosin administration into the AV3V region prevents the baroreceptor-mediated fall in heart rate evoked by increased blood pressure during intravenous infusion of hypertonic saline (5). The present experiments found that prazosin increases basal heart rate, which could be due to decreased parasympathetic drive and/or increased cardiac sympathetic nervous system tone. However, the precise relationship between AV3V $\alpha_1$- and $\alpha_2$-adrenergic receptors, norepinephrine release, and parasympathetic/sympathetic balance to the heart is currently unknown.

In summary, these experiments have demonstrated that local administration of HT aCSF to the AV3V region enhances the cardiac component of the baroreflex during acute hypertension induced by intravenous phenylephrine. Furthermore, the increased bradycardia during HT aCSF is due to stimulation of $\alpha_2$-adrenergic receptors in the AV3V region. However, the precise contribution of increased parasympathetic and/or decreased sympathetic cardiac drive during $\alpha_2$-adrenergic receptor stimulation in the AV3V region is not known.
Perspectives

The results from these experiments demonstrate that the AV3V region has a critical role in modulation of cardiac baroreflex sensitivity during hypertonic conditions. These results extend findings from earlier studies demonstrating that this brain area mediates the decreased baroreflex sensitivity characteristic of angiotensin II infusion (4). These data suggest that although the AV3V area does not entirely control baroreflex-induced changes in heart rate, this brain region is a hypothalamic site critical in modifying the gain of cardiac baroreflex-induced responses in certain experimental conditions. Furthermore, at least for hyperosmolality, this effect is mediated by stimulation of α2-adrenergic receptors.

Nonuniform responses by components of the autonomic nervous system occur during several experimental treatments (11, 29). The selective effects of AV3V tissue on baroreflex-induced responses in heart rate, while not altering RSNA responses, are similar to results observed following chronic infusion of hypertonic saline into the third ventricle (10). Central anatomic differentiation of control circuits for individual components of the autonomic nervous system may account, at least in part, for the complex, regionally specific patterns of peripheral autonomic nerve responses produced during certain experimental manipulations (11, 29). Furthermore, CNS anatomic specificity could contribute to the qualitatively dissimilar responses in heart rate observed during activation of the baroreceptors and during other conditions associated with increased blood pressure, such as the defense reaction. The present experiments demonstrate that AV3V periventricular tissue contains structures that may contribute to selective, specific changes in heart rate.

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