Effects of Lateral Parabrachial Nucleus Lesions in Chronic Renal Hypertensive Rats


Abstract

Neuroanatomic studies describing forebrain projections to the lateral parabrachial nucleus suggest a central integrative role in cardiovascular regulation. We performed this study to examine the role of this pontine nucleus in the maintenance of one-kidney, figure-8 renal-wrap hypertension. Bilateral ibotenic acid ablation of the lateral parabrachial nucleus was performed 4 weeks after induction of hypertension or sham operation. In hypertensive rats, ablation produced a significant reduction in mean arterial pressure from 160±4 to 118±2 mm Hg and a transient but significant increase in heart rate from 381±5 to 408±8 beats per minute on the first day after ablation; arterial pressure returned to preablation values by day 5 after ablation. In sham-operated, normotensive animals, arterial pressure was not altered by ablation, and a transient but significant increase in heart rate from 384±8 to 419±7 beats per minute was again observed. Before ablation, trimethaphan administration produced a significantly greater drop in arterial pressure in hypertensive (Δ−72.8±4.6 mm Hg) versus normotensive (Δ−55.7±4.1 mm Hg) animals. This effect was eliminated on day 1 after ablation yet returned on day 4 after ablation. In blood samples obtained before ablation and on days 1 and 4 after ablation, circulating plasma catecholamine concentrations in both groups remained unchanged. These observations suggest that, because of possible alternate neural compensatory mechanisms, lateral parabrachial nucleus ablation produces a significant yet transient reversal of renal-wrap hypertension. Thus, the lateral parabrachial nucleus may contribute to the increased sympathetic nervous system function associated with this model.

Key Words • paraventricular hypothalamic nucleus • hypertension, renovascular • ibotenic acid • kidney function

The initiation of sodium-dependent hypertension appears to be related to a reduction in renal function contributing to decreased sodium excretion. Alterations in body fluid sodium concentration may lead to a stimulation of central neural mechanisms. In particular, stimulation of sodium-sensitive sites in the hypothalamus and subsequent pathways through the hypothalamic paraventricular nucleus (PVN) may result in the activation of peripheral neural mechanisms, leading to the increased vascular resistance that accompanies sodium-dependent hypertension. The PVN may play a role in the development and maintenance of experimental hypertension. Lesion studies have demonstrated that an exaggerated sympathetic nervous system function contributes to an elevated arterial pressure as observed in Dahl salt-sensitive, deoxycorticosterone-saline, and spontaneously hypertensive rat models of hypertension. Furthermore, this laboratory has recently demonstrated that PVN ablation acutely reverses one-kidney, figure-8 renal-wrap hypertension in rats by interfering with an increased functional sympathetic nervous system associated with this animal model.

Neuroanatomic and functional data further suggest an integrated involvement of the pontine lateral parabrachial nucleus (LPBN) in the descending hypothalamic regulation of peripheral vascular resistance because reciprocating neuronal projections to many forebrain nuclei, including the PVN, have been demonstrated. Indeed, descending projections from the LPBN have been shown to extend primarily to the rostroventrolateral medulla (RVLM) to activate the sympathetic nervous system. In addition, an integration of cardiovascular information between the PVN and LPBN has been further demonstrated where LPBN ablation prevents PVN-stimulated alterations in sympathoadrenal activity. Because of these observations, the goal of the present study was to further elucidate the possible contribution of the LPBN to the maintenance of elevated arterial pressure in the renal-wrap hypertensive rat.

Methods

Animals and Surgical Preparation

Studies were performed according to the “Guiding Principles in the Care and Use of Animals” of the American Physiological Society. Methoxyflurane-anesthetized rats (225 to 250 g) were subjected to a one-kidney, figure-8 renal-wrap combined with contralateral nephrectomy (n=17) in a procedure described previously. Rats undergoing unilateral nephrectomy alone (n=19) served as sham-operated controls. After 4 weeks, rats were anesthetized with pentobarbital (50 mg/kg IP, Abbott Laboratories) and chronically prepared with bilateral stainless steel LPBN cannulas as well as femoral arterial and venous catheters for the measurement of mean arterial pressure (MAP) and heart rate (HR) and for injection of drugs, respectively. LPBN cannula placement was determined with the use of a standard atlas coordinate system (AP, −9.2 mm from bregma; ML, ±2.4 mm from midsagittal sinus; DV, 5.9 mm from dura). Rats were individually housed in wire mesh cages and allowed free access to standard
Laboratory chow (0.1 mmol sodium/g) and distilled water throughout the protocol. A minimum of 3 postsurgical recovery days was allowed before any experimentation. Parameters analyzed were MAP (millimeters of mercury), HR (beats per minute [bpm]), fluid balance (milliliters; this parameter considers only daily water intake and urinary output and does not reflect loss by respiration or feces), hematocrit, body weight (grams), urinary sodium excretion (millimoles per day), urinary potassium excretion (millimoles per day), plasma sodium (millimoles per liter), plasma potassium (millimoles per liter), plasma epinephrine (picograms per milliliter), and plasma norepinephrine (picograms per milliliter). MAP and HR (triggered by the arterial pressure pulse) were analyzed daily for 20-minute periods at a rate of 4 Hz using a MacLab A/D system (model 8).

Protocol

Control measurements of all parameters were obtained in all animals. Rats were then anesthetized with pentobarbital and subjected to either bilateral ibotenic acid (Sigma Chemical Co) lesions of the LPBN (n=30) or bilateral ibotenic acid lesions of the Kölliker-Fuse (KF) nucleus (n=6) to serve as a control for LPBN ablation. Ibotenic acid (10.0 µg/µL) was dissolved in sterile saline and administered bilaterally in a volume of 0.5 µL per site. After LPBN ablation daily measurements were obtained for an additional 5 days. Additional blood samples were collected for determination of plasma catecholamines only on days 1 and 4 after ablation. During the control day and days 1 and 4 after ablation, the sympathetic components of MAP and HR were assessed by administration of the short-acting ganglionic blocking agent trimethaphan camsylate (1.0 mg/min). These responses were compared with consistent depressor responses to short-term infusion of sodium nitroprusside (10.0 µg/min).

On day 5 after ablation the neurohumoral maintenance of MAP and HR was further assessed by pharmacologic blockade. The drug protocol used to assess the contributions of the sympathetic nervous system, renin-angiotensin system, and arginine vasopressin system consisted of sequential administration of pharmacologic antagonists. The contribution of the sympathetic nervous system was examined by autonomic blockade with hexamethonium (25 mg/kg) and atropine (0.4 mg/kg). The contribution of the renin-angiotensin system was examined by administration of the angiotensin I-converting enzyme inhibitor enalaprilat (1.0 mg/kg). The contribution of the arginine vasopressin system was tested by administration of the V1 antagonist d(CH2)5Tyr(Me)arginine vasopressin (10.0 µg/kg). The antagonists were consistently administered in this order. Injections of phenylephrine (3.0 µg/kg), angiotensin I (100 ng/kg), and arginine vasopressin (15.0 mU/kg) were used to test the effectiveness of the respective system blockade.

Histology

Once experiments were concluded, animals were deeply anesthetized with pentobarbital and perfused transcardially with isotonic saline followed by 10% buffered formalin for 10 minutes. Brains were removed and stored in 10% buffered formalin for at least 24 hours before sectioning. Sections were then cut on a freezing microtome at 60-µm intervals and stained with cresyl violet for determination of the extent of neuronal damage in animals with ibotenic acid ablations. Effective ablations were determined by composition examina-
Photomicrographs show identification of ablation sites in 60-μm cresyl-stained histologic coronal brain slices. A, Normal lateral parabrachial nucleus (LPBN); B, ibotenic acid-ablated LPBN; C, ibotenic acid-ablated Kölliker-Fuse (KF) nucleus. VSC indicates ventral spinocerebellar tract; LC, locus coeruleus; 4V, fourth ventricle; SCP, superior cerebellar peduncle; and Me5, mesencephalic tract of the trigeminal nerve.

Statistical Analysis

All values presented are mean±SEM. Within- and between-group differences were evaluated with a mixed-design ANOVA. Individual post hoc comparisons of means within a variable were performed with the Newman-Keuls and t test. Probability levels of less than .05 were considered significant.

Results

Rats administered ibotenic acid recovered rapidly with no significant weight loss during the protocol. LPBN lesions were stereotaxically directed to the external and central aspects of the nucleus. In general, for this study the lesion was required to include at least 80% of the nucleus, anterior-posterior. All animals presented in this investigation met this criterion. Fig 1 demonstrates the histological assessment of the common area of ablated tissue throughout the rostral-caudal extent of the LPBN. Fig 2A shows a nonablated LPBN, and Fig 2B represents an ibotenate-ablated nucleus near the same rostral-caudal aspect. The lesion resulted in a loss of tissue, including much of the external lateral portion of the nucleus and extending to the boundaries of the ventral medial nucleus. In most cases there was also slight mechanical damage to the overlying cerebellum caused by cannula placement. Ibotenate damage to the medial parabrachial nucleus was minimized because of the presence of the apparent natural barrier provided by the brachium of the superior cerebellar peduncle. Microscopic visualization of the presence of macrophage and glial infiltration as well as area edema or loss of cell nuclei was also used to evaluate damaged areas. As controls for LPBN-ablated animals, Fig 2C shows a section from one animal subjected to bilateral KF ablation.

As shown in Fig 3, in renal-wrapped hypertensive rats LPBN ablation produced a significant reduction in MAP from 160.4±4.0 to 117.6±1.9 mm Hg (df=13, F=68.0) and a transient but significant increase in HR from 380.6±4.8 to 408.0±7.9 bpm (df=13, F=7.2) on the first day after LPBN ablation. MAP remained significantly attenuated compared with the control day for 3 additional days but returned to preablation values by day 5 after ablation. In sham-operated normotensive animals LPBN ablation did not alter MAP (df=15,
TABLE 1. Daily Water Intake and Balance, Urine Output and Sodium Excretion, Plasma Sodium, and Catecholamine Data for Hypertensive and Normotensive Lateral Parabrachial Nucleus-Ablated Rats

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Wrap indicates hypertensive rats (n=10); Sham, normotensive rats (n=13). Values are mean±SEM.

*Significant difference from control (P<.05).

F=0.89), and a transient but significant increase in HR from 384.3±7.5 to 419±6.5 bpm was again observed (df=15, F=3.21). As shown in Table 1, urinary sodium excretion and plasma sodium, epinephrine, and norepinephrine were not significantly altered by LPBN ablation and remained unchanged throughout the protocol in both hypertensive (df=10) and normotensive (df=11) animals. Urinary potassium excretion, plasma potassium, and hematocrit were similarly unaltered (data not shown). However, a significant increase in fluid balance was noted in both hypertensive (12.0±1.8 to 25.5±2.4 mL) (df=10, F=1.41) and normotensive (12.4±1.8 to 26.1±1.7 mL) (df=12, F=1.61) animals on day 1 after LPBN ablation. The elevated positive fluid balance in these animals was due to an increased water intake because urinary output remained constant on all days.

Results of the determination of sympathetic control of MAP and HR performed during the control day and days 1 and 4 are shown in Fig 4. Ganglionic blockade with trimethaphan produced a fall in MAP in hypertensive animals (Δ−72.8±4.6 mm Hg, n=6) that was significantly greater (P<.05) than that produced in normotensive animals (Δ−55.7±4.1 mm Hg, n=7). This effect was eliminated on day 1 after LPBN ablation but returned on day 4 after ablation. MAP and HR responses to nitroprusside infusion were not different between or within the two groups over the 3 days.

Pharmacologic blockade of the sympathetic nervous system, renin-angiotensin system, and arginine vasopressin system was performed on day 5 after ablation; the effects on MAP and HR in both hypertensive (n=12) and normotensive (n=14) LPBN-ablated animals are shown in Table 2. Although initially a statistically significant difference in blood pressure existed during the control day, blockade of autonomic ganglia eliminated this between-groups difference. Combined angiotensin-converting enzyme inhibition and V1 receptor antagonism produced a similar further lowering of arterial pressure in both rat groups. HR was significantly reduced by this treatment only in the hypertensive animals. LPBN ablation did not alter these parameters in normotensive sham renal-wrapped animals.

Normotensive KF-ablated animals also demonstrated no significant alterations in MAP and HR or any other measured parameter throughout the protocol (data not shown). Hypertensive KF-ablated animals only demonstrated a significant increase in HR on day 1 after ablation. Additionally, the effects of nitroprusside and trimethaphan on MAP and HR responses in these two groups were not altered throughout the protocol as a result of KF ablation. Pharmacologic blockade on day 5 after ablation produced responses similar to those observed in hypertensive and normotensive LPBN-ablated animals.

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Discussion

The data from this study suggest that focused bilateral ablation of the pontine LPBN transiently attenuates chronic one-kidney, figure-8 renal hypertension. On the first day after LPBN ablation, MAP in hypertensive animals was significantly reduced to normotensive levels. Arterial pressure gradually increased from day 2 to day 5 after ablation, when it returned to preablation hypertensive levels. In contrast, the blood pressures of sham-operated normotensive animals were unaffected by LPBN ablation. The arterial pressures of renal-wrap hypertensive animals remained similarly unaffected throughout the protocol in response to KF ablation.

A salt sensitivity in certain human hypertensive populations has also been noted in several rat models of hypertension, including the Grollman hypertensive rat. A relation between altered physiological sodium concentrations and an activation of sites in the rostral hypothalamus has been widely suggested. Neural pathways through the PVN appear to be an important component in mediating the response of the sympathetic nervous system to sodium. For example, several functional studies have shown that electrical or chemical stimulation of the PVN can produce significant alterations in arterial blood pressure via activation of the sympathoadrenal nervous system. Conversely, electrolytic or chemical ablation of the PVN has been shown to attenuate the development of the rise in arterial pressure in spontaneously hypertensive, deoxycorticosterone-salt, and Dahl salt-sensitive hypertensive animal models; PVN lesions also reverse the hypertension associated with aortic baroreceptor deafferentation and renal-wrap hypertension in the rat. Thus, these manipulations may interfere with hypothalamic regulation of central sympathetic activity.

Descending neural pathways from the PVN have been demonstrated to project to three areas that regulate cardiovascular activity: the intermediolateral cell column, where preganglionic sympathetic neurons are located; the RVLM, which may be the principal vasomotor center; and the LPBN, which has reciprocal connections with the PVN and also sends projections to the RVLM. The effectiveness of LPBN ablation in reversing renal-wrap hypertension may therefore depend on the association of this nucleus with a pathway between the PVN and RVLM. A recent study from this laboratory has shown that LPBN ablation effectively inhibits the excitatory cardiovascular responses to glutamate stimulation of the PVN in conscious rats. Thus, the results in the present study are consistent with the suggestion that the antihypertensive effect associated with ablation of the PVN is through an interference with the sympathetic nervous system. Additionally, because an augmented sympathetic nervous system function has been demonstrated in the renal-wrap hypertensive rat, the present findings further indicate that a reduced sympathetic function could account for the fall in arterial pressure on day 1 after ablation. In contrast to

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GB indicates ganglionic blockade; ENAL, enalapril; AVP-X, vasopressin receptor antagonist; Wrap, hypertensive rats (n=12); and Sham, normotensive rats (n=14). Values are mean±SEM.

*Significant difference from Sham group.
†Significant difference from control (P<.05).
other models of hypertension, the reversal of hypertension by LPBN ablation in this study was transient because MAP returned to preablation levels by day 5 after ablation. Compared with normotensive animals, MAP and HR responses to the ganglionic-blocking drug trimethaphan in hypertensive rats were significantly reduced on the day after LPBN ablation compared with responses during the control period. The disparity in response returned on day 4 after ablation, suggesting that the recovery of hypertension was primarily neurogenically mediated. On day 5 after ablation, when hypertension had fully recovered in wrapped animals, MAP and HR responses to ganglionic blockade with hexamethonium and atropine were again augmented in hypertensive compared with normotensive animals. Pharmacologic antagonists to the renin-angiotensin system and vascular vasopressin receptors also affected MAP in the same manner in both rat groups, indicating that neither of the mechanisms contributed to the postablation return of arterial pressure in hypertensive animals.

The recovery of hypertension in renal-wrapped animals after PVN ablation could be attributed to sodium retention where the postablation fall in MAP reduces renal perfusion pressure, thereby decreasing renal sodium excretion. Such responses were not noted in the current study because, despite LPBN ablation, both plasma and daily urinary electrolyte concentrations remained unchanged. Previous reports indicate that the LPBN is important in the regulation of fluid intake such that electrolytic and chemical lesions of the LPBN elicit a short-term enhancement in drinking behavior. The results of the present study also demonstrate that a twofold increase in water intake and fluid balance occurred on day 1 after LPBN ablation. As fluid retention was observed in both normotensive and hypertensive rats, it probably did not contribute to the restoration of hypertension.

The KF ablation studies demonstrate the specificity of the blood pressure-lowering effects of LPBN ablation. In the present study, independent of any effect on MAP, transient increases in HR on day 1 after ablation in both normotensive, LPBN-ablated and hypertensive, KF-ablated animals were observed. Both the KF nucleus and LPBN have been shown to have reciprocal connections with the nucleus tractus solitarius, suggesting that these specific central ablations may interfere with ascending or descending cardiovascular regulatory influences of the nucleus tractus solitarius on the baroreceptor reflex. Additionally, the possibility that ibotenate may transiently lower blood pressure through the stimulation of tissue in or around the LPBN is not currently supported by the literature because ibotenate has been shown to produce substantial selective lesions of nerve cells but not axons of passage. Furthermore, recovery of cell function after exposure to ibotenate, as reflected by the return of enzymatic activity such as glutamate decarboxylase or choline acetyltransferase, has not been demonstrated.

In summary, a role for the LPBN in renal hypertension is implicated because chemical ablation of the LPBN transiently reduces renal-wrap hypertension. During the control day and day 4 after ablation, an increase in central sympathetic function, independent of any sympathoadrenal response, solely contributes to the disparity in MAP between wrapped and sham-operated animals. Ablation of the LPBN may interfere with descending hypothalamic regulation of sympathetic function and peripheral autonomic tone.

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