Acute Fulminating Neurogenic Hypertension Produced by Brainstem Lesions in the Rat

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ABSTRACT
Bilateral electrolytic lesions of the nucleus tractus solitarii in the rat at the level of the obex abolished baroreceptor reflexes and resulted in an immediate, marked elevation in systemic blood pressure without a change in heart rate. In unanesthetized rats the hypertension was associated with a marked increase in total peripheral resistance, a reduction in blood flow in the abdominal aorta, and an increase in central venous pressure. The cardiac output was reduced to 62% of control as a consequence of reduced stroke volume, which was reflected, in turn, by increased end-diastolic pressure. The hypertension was abolished and the end-diastolic pressure lowered by blockade of alpha receptors with phentolamine. The hypertension was not due to changes in blood gases or to release of agents from the kidneys or the adrenal glands; it was very sensitive to anesthetics and was abolished or aborted by midcollicular decerebration. Within hours after lesioning, the rats developed progressive congestive heart failure and died in shock, often in association with pulmonary edema. We concluded that the fulminating hypertension evoked by lesions of the nucleus tractus solitarii was due to the increased vasoconstriction caused by the augmented discharge of sympathetic nerves in response to central deafferentation of baroreceptor reflexes; the hypertension was mediated by alpha receptors and depended on the integrity of structures lying above the midbrain.

KEY WORDS
systemic vasoconstriction
depressor nerves
cardiac failure
nucleus tractus solitarii
vasomotor centers
vasoconstriction
baroreceptors
pulmonary edema

The failure of such lesions to produce hypertension might be due to the fact that lesions destroy neurons mediating both the pressor and the depressor components of baroreceptor and chemoreceptor reflexes. Also, anesthesia or decerebration might mask any hypertensive response resulting from the lesions.

In this study, we attempted to produce hypertension in chronically prepared unanesthetized rats by bilateral electrolytic lesions of the NTS. We demonstrated that acute fulminating hypertension, often culminating in pulmonary edema, could be produced by such lesions.

Methods
These experiments were performed on male Sprague-Dawley rats (300–400 g) housed four to six in a cage in a thermostatically regulated room (20°C) with cycled lighting (on at 7 AM, off at 7 PM). They were provided with lab chow and water ad libitum. All rats were anesthetized with 2% halothane in 100% O2 blown over the nose through a face mask. In most rats, a polyethylene catheter (PE50, 0.023 inches, i.d.) filled with heparinized saline (20 units/ml) was inserted in the ventral artery of the tail or the femoral artery for direct measurement of intra-arterial blood pressure. The catheter was fixed to soft tissue with sutures and connected to a strain-gauge transducer (Statham 584).
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P23Db). Pressure measurements were displayed on a polygraph (Beckman Dynograph recorder 504A). Heart rate was computed from the blood pressure pulse wave by a cardiotachometer (Beckman 9857) and was simultaneously displayed. At this time, in selected rats, cannulas or probes for measuring cardiac output, aortic blood flow, left ventricular pressure, and central venous pressure were inserted. In most cases the anesthesia was then discontinued, and the rat was permitted to recover for 30 minutes. Base-line measurements of arterial blood pressure and heart rate were obtained in the quiet, awake state. The rat was then reanesthetized to place the brainstem lesions.

**PRODUCTION OF HYPERTENSION BY LESIONS OF THE NUCLEUS TRACTUS SOLITARIUS**

The rat was placed in a stereotaxic frame with the head flexed to 45°. The region of the obex was exposed by a limited occipital craniotomy. In some rats, a small portion of the posterior vermis of the cerebellum was removed by suction to facilitate exposure. A thin monopolar electrode consisting of a stainless steel wire (diameter 0.006 inches) coated with Teflon, bored at the tip (0.2 mm), and carried in a stainless steel hypodermic needle (no. 28) was placed in the brainstem by a micromanipulator. The lesion was made by passing an anodal d-c current of 5 ma for 1-3 seconds. The cathode was a clip placed in an adjacent muscle. The electrode was removed, and a lesion was then placed at a symmetrical site on the other side of the brainstem.

Several types of operated control rats were prepared. Sham operations were performed by exposing the brainstem and placing the electrode in the region of the NTS bilaterally without making lesions. In other controls subjected to surgery, bilateral lesions were placed in regions other than the NTS, usually laterally in the cuneate nucleus, ventrally in the medial reticular formation (sometimes including the raphé nuclei), or in the area postrema.

After surgery the wounds were closed and infiltrated with 2% procaine to minimize pain, and the rat was removed from the stereotaxic frame for further observation. When cardiovascular events were monitored, the rat was placed in a small cage through which cannulas or probes were led to appropriate connectors. Cardiovascular activity was measured within 30 minutes after cessation of anesthesia. At this time the rats were quiet, cardiovascular activity was reasonably stable, and, in rats with NTS lesions, the hypertension was well developed.

**MEASUREMENT OF CARDIOVASCULAR ACTIVITY**

Cardiac output was measured by a thermal dilution technique (7, 18, 19). A small thermister (Hewlett-Packard model 14012) was threaded down the common carotid artery and was lodged at the aortic arch just above the aortic valve. Normal saline (0.1 ml) at room temperature was injected as a bolus into the right atrium from a polyethylene catheter of known fluid capacity threaded up the femoral vein (20). The thermal dilution curve was displayed on the polygraph. A significant recirculation of the thermal indicator occurred as evidenced by a change in the slope of the downstroke of the temperature curve (18). To eliminate any contribution of recirculation to the calculation of cardiac output, the curve was replotted on semilogarithmic paper, and the area under the curve was measured by a planimeter (7, 18). Cardiac output was then calculated according to the method of Cooper et al. (18):

$$ CO = \frac{Q(T_a - T)k}{T_t} $$

where $CO$ = cardiac output (ml/min), $Q$ = quantity of injectate (ml), $T_a$ = temperature of injectate (°C), $T_t$ = temperature of blood (°C), $t$ = time (seconds), $(T_a - T)$ = area under curve, and $K$ = a constant.

The values used for specific gravity and specific heat of rat blood were those cited by Cooper et al. (18).

Stroke volume was calculated by dividing cardiac output by heart rate.

Abdominal aortic blood flow was recorded by a square-wave electromagnetic flow meter. Through a laparotomy a flow probe 3 mm in circumference was applied to the abdominal aorta just below the origin of the renal arteries, and the incision was closed. The zero level of the flowmeter was determined by established methods and reconfirmed in situ at the end of the experiment after the rat was dead. The flow probe was recalibrated by passing whole blood through the probe at a constant rate (21, 22).

Total peripheral resistance (TPR) was calculated from the formula:

$$ TPR = \frac{(P_m - CVP)}{CO}, $$

where $CVP$ = central venous pressure measured from the right atrium and $P_m$ = mean arterial blood pressure.

$$ P_m = \frac{(P_s + 2P_d)}{3}, $$

where $P_s$ = systolic pressure and $P_d$ = diastolic pressure. Regional vascular resistance (RVR) was calculated from the formula:

$$ RVR = \frac{P_m}{F_m}, $$

where $F_m$ = mean blood flow in the abdominal aorta.

Left ventricular pressure was measured through a polyethylene catheter (PE50, 0.023 inches, i.d.) threaded down the right common carotid artery into the left ventricle and connected to a Statham P23Db transducer.

Central venous pressure was measured through a polyethylene catheter threaded up the femoral vein into the right atrium.

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**BLOOD GAS ANALYSIS**

Po2 and Pco2 were measured in 100-μliter samples of arterial blood collected in heparinized capillary tubes (Radiometer type D5511/12.5, 100 μliters) from the catheter placed in the ventral tail artery. The Po2 and Pco2 were measured in duplicate in a Radiometer Blood Microsystem (type BMS3) (23).

**OTHER PROCEDURES**

Decerebration was performed at the midcollicular level in anesthetized rats with a small blunt spatula inserted through a burr hole placed in the parietal bone. The cerebellum was removed by suction through a limited occipital craniotomy. The kidneys, the adrenal glands, or both were removed through a lateral flank incision. After placing ligatures around the renal hilus, the organs were removed en bloc without decapsulation of the kidney.

To test the baroreceptor reflexes, norepinephrine or angiotensin II, in a volume never exceeding 0.2 ml, was injected intravenously into a catheter in the femoral vein. The dose was sufficient to evoke a submaximal pressor response. These procedures were performed with the rat lightly anesthetized with alpha-chloralose (30 mg/kg, iv) to obtain a more stable blood pressure without impairing cardiovascular reflexes.

**POSTMORTEM EXAMINATION**

An autopsy was performed in rats that died spontaneously or were killed by an overdose of sodium pentobarbital (20 mg, ip). After ligation of the inferior and superior caval veins, ascending aorta, and trachea, the lungs and the heart were removed from the body and weighed. The lung weight–body weight ratio (× 100) was used to assess the presence of pulmonary edema (24).

**HISTOLOGICAL EXAMINATION OF BRAIN AND OTHER ORGANS**

At the termination of the experiment the brain was excised and, along with other organs, placed in 10% formalin for at least 2 weeks. The localization of brain lesions was confirmed on frozen sections cut every 50μ and stained for cells by the Nissl method (14). The lung and the heart were blocked, embedded in paraffin, and stained with hematoxyline and easin.

**STATISTICAL EVALUATION**

The significance of changes in cardiovascular and other parameters resulting from brain lesions was estimated by a paired t-test (25) in which postlesion and prelesion measurements were compared. P < 0.05 was significant.

**Results**

**Effects of Acute Lesions of the Nucleus Tractus Solitarii on the Blood Pressure, Heart Rate, Respiratory Rate, and Other Autonomic Responses.—**Small bilateral electrolytic lesions of the dorsal brainstem that destroyed the NTS at the level of the obex invariably resulted in arterial hypertension (Fig. 1). The hypertension appeared within 5 minutes after the halothane anesthesia was stopped, and within 20–30 minutes hypertension was stable and sustained until the onset of heart failure. By 30 minutes after termination of anesthesia, the systolic, diastolic, and pulse pressures were significantly increased and unassociated with changes in heart rate (Table 1 and Fig. 1). The respiratory rate was generally reduced at this time to 85% of control (Table 1). The rats with NTS lesions were hypoactive, normothermic, and had no signs of any generalized increase in sympathetic activity such as proptosis, mydriasis, or piloerection.

**Localization of Effective Lesions.**—In all instances the electrolytic lesions of the brainstem effective in producing hypertension destroyed the bulk of the NTS and the adjacent solitary tract bilaterally at the level of the obex (Fig. 2 and Fig. 3a and b). The adjacent parahypoglossal area (26) and the dorsal motor nucleus of the vagus were variably damaged. Lesions primarily damaging the parahypoglossal areas with little damage to the NTS did not produce the syndrome. Partial lesions of the NTS, which often spared more lateral portions of the nucleus and the tract, were not sufficient to produce hypertension (Fig. 3c). Therefore, a critical mass of the NTS, or perhaps a specific portion of the nucleus and tract, apparently had to be destroyed bilaterally to produce hypertension. Moreover, damage to the parahypoglossal area was not, by itself, sufficient to produce hypertension. Unilateral NTS lesions resulted in a
**BRAINSTEM LESIONS AND HYPERTENSION**

**TABLE 1**

Effects of Bilateral Lesions of the Nucleus Tractus Solitarii in Rats on Cardiovascular Dynamic, Respiration, and Blood Gases

<table>
<thead>
<tr>
<th></th>
<th>Postlesion</th>
<th>% of control</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic pressure (mm Hg)</td>
<td>201 ± 5</td>
<td>161</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Diastolic pressure (mm Hg)</td>
<td>151 ± 3</td>
<td>155</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Pulse pressure (mm Hg)</td>
<td>90 ± 4</td>
<td>179</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Mean pressure (mm Hg)</td>
<td>188 ± 3</td>
<td>158</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>430 ± 13</td>
<td>105</td>
<td>n.s.</td>
</tr>
<tr>
<td>Cardiac output (ml/min)</td>
<td>74 ± 3</td>
<td>62</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Stroke volume (ml/beat)</td>
<td>0.17 ± 0.01</td>
<td>59</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Central venous pressure (cm Hg)</td>
<td>4.4 ± 0.1</td>
<td>244</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Total peripheral resistance (mm Hg min/ml)</td>
<td>2.376 ± 0.126</td>
<td>255</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Left ventricular end-diastolic pressure (mm Hg)</td>
<td>49.5 ± 5</td>
<td>326</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Abdominal aortic flow (ml/min)</td>
<td>73.7 ± 1.1</td>
<td>82</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Abdominal aortic resistance (mm Hg min/ml)</td>
<td>23.8 ± 4.1</td>
<td>301</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Respiratory rate (breath/min)</td>
<td>53 ± 3</td>
<td>85</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>92.1 ± 1.4</td>
<td>99</td>
<td>n.s.</td>
</tr>
<tr>
<td>Arterial Po2 (mm Hg)</td>
<td>42.6 ± 1.6</td>
<td>107</td>
<td>n.s.</td>
</tr>
</tbody>
</table>

All values are means ± se. Measurements in control rats and in rats with NTS lesions were taken 30 minutes after cessation of anesthesia. Statistical evaluation was made using a paired t-test (2) relating postlesion values to control values. n.s. = not significant.

Small but significant elevation of blood pressure above control. However, these rats survived over 24 hours, at which time blood pressure measured directly had returned to normal.

Lesions in adjacent areas of the medulla including the cuneate nuclei (Fig. 3d), the raphe nucleus (Fig. 3e), and paramedial sites of the reticular formation (part of the so-called depressor zone [27]) (Fig. 3e) did not produce hypertension. Lesions of the area postrema also did not affect blood pressure.

**FIGURE 2**

Representative lesion of the brainstem in a rat that produced fulminating neurogenic hypertension. This section was taken just rostral to the obex. Nissl stain; bar represents 1 mm. See Figure 3 for identification of the nuclear groups.

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Cardiodynamic Changes during the Acute Hypertensive Stage.—We next sought to establish whether the acute hypertension produced by NTS lesions was due to an increase in total peripheral resistance or to an increase in cardiac output. Since arterial hypertension was fully developed in the lesioned rat immediately after halothane was stopped (Fig. 1), cardiovascular activity was measured within the first 30 minutes after discontinuing the anesthesia when the rat was hypomotile but well established in arterial hypertension.

The cardiodynamic changes associated with the hypertension induced by bilateral lesions of the NTS are listed in Table 1. The elevated arterial blood pressure was accompanied by an increase in the total peripheral resistance to 255% of control and a tripling of the resistance in the abdominal aorta. The increased aortic resistance, in large measure, reflected the increased resistance in arteries to muscle and skin of the trunk and lower extremities. Aortic blood flow was reduced by 35%. In contrast to the increase in total peripheral resistance, the cardiac output was reduced to 62% of control (Table 1, Fig. 4). There was a 328% increase in left ventricular end-diastolic pressure, indicating decreased ventricular ejection (Table 1). The central
FIGURE 3
Representative brainstem lesions effective or ineffective in producing neurogenic hypertension in the rat. The lesions are projected on a cross section of the medulla of the rat at the level of the rostral third of the inferior olivary nucleus. Only one side of generally symmetrical lesions is shown. Lesions in a and b were associated with hypertension. The lesions in c, d, and e failed to produce hypertension. Abbreviations are according to Cragie (48): NC = nucleus cuneatus, NDM = dorsal motor nucleus of the vagus, NG = nucleus gracilis, NI = nucleus intercalatus, NOAM = nucleus olivaris accessorius, NOPD = nucleus olivaris principalis (pars dorsalis), NOPV = nucleus olivaris principalis (pars ventralis), NRL = nucleus reticularis lateralis, NRV = subnucleus reticularis centralis medullae oblongatae, NTS = nucleus tractus solitarii, R0 = nucleus raphé obscurus, RTBS = radix tractus spinalis nucleus trigemini, THSD = tractus spinocerebellaris dorsalis, Ts = tractus solitarius, XII = nucleus hypoglossi.

FIGURE 4
Changes in cardiac output, thermal dilution curves, heart rate, and systemic blood pressure before (A) and after (B) production of bilateral lesions of the NTS causing hypertension in the rat. During measurements the rat was unanesthetized. Before lesions were made, there was a significant recirculation apparent when the thermal dilution curve was replotted on a semilogarithmic paper (see Methods). The dotted line in A represents the curve corrected for recirculation. After bilateral lesions were made, there was practically no recirculation. The increased drop in temperature indicates that cardiac output decreased.

venous pressure measured in the right atrium was increased 244% (Table 1).

The arterial hypertension with the increased left ventricular end-diastolic pressure elicited by NTS lesions was promptly abolished by the systemic injection of the alpha-receptor blocking agent, phentolamine (1 mg/kg, iv). This finding indicates that the increased left ventricular end-diastolic pressure characterizing the acute hypertensive state resulted from an increased afterload that was, in tum, a consequence of the neurogenically mediated increase in peripheral vascular resistance.

Therefore, the hypertension produced by bilateral lesions of the NTS was primarily due to increased peripheral resistance, was neurogenic in origin, and was primarily mediated by alpha receptors.

Changes in Blood Gases during Acute Hypertension.—Because NTS lesions abolish chemoreceptor reflexes from carotid and aortic body chemoreceptors (17) and because the associated decrease in the respiratory rate could lead to a degree of asphyxia resulting in reflex hypertension (28, 29), arterial Po2 and Pco2 were measured in lesioned rats during the acute hypertensive phase. At the time the hypertension was well developed, the Po2 and Pco2 of arterial blood samples were unchanged. Moreover, administration of 100% O2 by a face mask did not result in attenuation of the hypertension. Thus the hypertension resulting from lesions of the NTS was not due to a reflex response to hypoxia.

Effect of Removal of Adrenal Glands and Kidneys.—The hypertension produced by NTS lesions cannot be attributed to release of pressor substances from the kidneys or the adrenal glands. The magnitude of the hypertension was unaffected by prior bilateral removal of the adrenal glands and the kidneys (Table 2).

Effects of Anesthesia on Acute Hypertension.—The hypertension produced by NTS lesions was extremely sensitive to anesthetic agents. It disappeared if the rats were reanesthetized with 2% halothane (Fig. 1), barbiturates (e.g., sodium pentobarbital 40 mg/kg, iv), or alpha-chloralose (50 mg/kg, iv).

Effects of Midcollicular Decerebration and Cerebellectomy.—Decerebration at the midcollicular level either abolished the hypertension produced by
TABLE 2

Effects of Decerebration, Cerebellectomy, and Adrenonephrectomy on the Mean Blood Pressure in Rats with Bilateral Lesions of the Nucleus Tractus Solitarii

<table>
<thead>
<tr>
<th>Operation</th>
<th>N</th>
<th>Control (mm Hg)</th>
<th>After NTS lesions (mm Hg)</th>
<th>After NTS lesions and operation (mm Hg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Decerebration</td>
<td>5</td>
<td>103 ± 3</td>
<td>155 ± 8*</td>
<td>100 ± 7</td>
</tr>
<tr>
<td>Cerebellectomy</td>
<td>5</td>
<td>108 ± 4</td>
<td>152 ± 6*</td>
<td>158 ± 5†</td>
</tr>
<tr>
<td>Adrenonephrectomy</td>
<td>4</td>
<td>100 ± 3</td>
<td>152 ± 2*</td>
<td>149 ± 2†</td>
</tr>
</tbody>
</table>

All values are means ± se. Control values refer to prelesional blood pressure taken 30 minutes after anesthesia was discontinued. The rat was reinsitized and bilateral lesions of the NTS were made. Anesthesia was then discontinued and blood pressure was measured 30 minutes later. The rat was once again anesthetized, the indicated operation was performed, and 30 minutes after discontinuation of anesthesia the blood pressure was again measured.

*Values differ from control values (P < 0.001).
†Values differ from control values (P < 0.001) but not from values after NTS lesions.

NTS lesions or, if performed before the NTS lesions were made, blocked the predictable development of hypertension (Table 2). This finding demonstrates that the lowering of blood pressure by decerebration in rats with NTS lesions was not the result of a nonspecific effect of cerebral injury or hemorrhage. Rather the finding indicates that the integrity of rostral brain areas was essential for the expression of the hypertension.

Effects of Lesions of the Nucleus Tractus Solitarii on Baroreceptor Reflexes.—Since lesions of the NTS in cats anesthetized with chloralose abolish the reflex hypotension and bradycardia evoked by stimulation of baroreceptors, we sought to determine if similar lesions in rats would also abolish the reflexes. The cardiovagal component of the baroreceptor reflexes, evoked by infusion of either norepinephrine (0.05-0.2 μg in 0.2 ml) or angiotensin II (0.05-0.2 μg in 0.2 ml), was examined in five rats lightly anesthetized with alpha-chloralose (30 mg/kg, iv). Injection of 0.05-0.2 μg of either drug elicited reflex bradycardia associated with hypotension (Fig. 5). Before NTS lesions, all rats showed a typical graded bradycardia. After the lesions, the reflex bradycardia was completely abolished in all rats, and sometimes the heart rate response was reversed to tachycardia. These findings indicate that the NTS lesions effective in producing hypertension abolished baroreceptor reflexes.

Natural History of Hypertension.—All rats with adequate bilateral lesions of the NTS died within 8 hours. Before death the rats had labored breathing, audible gurgling rales, wheezes, and occasionally pink frothy fluid in their nostrils. At postmortem examination the rats had boggy lungs with frothy fluid often filling the trachea and bronchi. In most rats the lungs were characterized by moderate to intense interstitial edema, especially perivascular edema, congestion, and partial atelectasis. Intrapulmonary edema was often seen.

![Figure 5](http://circres.ahajournals.org/)

Reflex bradycardia and systemic hypertension evoked by intravenous injection of different doses of norepinephrine (NE) and angiotensin II before (A) and after (B) production of bilateral lesions of the NTS in the anesthetized rat (alpha-chloralose 30 mg/kg, iv). Before lesions, both agents produced a graded bradycardia associated with hypertension. After lesions, the reflex bradycardia was no longer elicited, and tachycardia and arrhythmias were observed with injections of norepinephrine and angiotensin II.
To determine the nature of the cardiovascular events leading up to the development of the pulmonary edema, we followed the change in blood pressure and heart rate in 11 rats from the time of lesioning until death. All had indwelling catheters in their ventral tail arteries. A representative example of this experiment is shown in Figure 6. After reaching a hypertensive plateau the systolic blood pressure gradually declined in association with a smaller drift in the diastolic pressure and a narrowing of the pulse pressure. During this period there was a small reduction in heart rate. Blood pressure fell precipitously 3–4 hours later, the clinical signs of pulmonary edema suddenly appeared and death ensued. All 11 rats died spontaneously within 5 hours. Ten rats had clinical evidence of pulmonary edema shown by their increased lung weight-body weight ratio (1.17*0.11) which was significantly different from that of 12 normal control rats (0.77 ±0.12, P<0.01) killed by an overdose of sodium pentobarbital (80-100 mg, ip).

**Discussion**

**PERIPHERAL MECHANISMS**

This study demonstrated that bilateral lesions of the NTS at the level of the obex in rats invariably resulted in the appearance of a syndrome of acute arterial hypertension. The elevation of blood pressure began almost immediately after placement of the lesions and discontinuation of anesthesia. The hypertension was neurogenic and resulted from an increased peripheral vascular resistance, which was due to intensive vasoconstriction secondary to augmented discharge of sympathetic preganglionic neurons. A similar mechanism also underlies the hypertension evoked by baroreceptor denervation in the rat (8). The vasoconstriction in our rats was probably mediated by alpha receptors, since the hypertension was blocked by the administration of phentolamine (30). Humoral agents released from the kidneys or the adrenal glands did not significantly contribute to the syndrome, at least not in the acute stage, since the magnitude of hypertension was unaltered by the removal of these organs.

The discharge of sympathetic preganglionic fibers was differentiated, not generalized, since there was no evidence of any associated mydriasis, proptosis, or hyperhydrosis at the time of maximal sympathetic engagement of the circulation. In addition to constriction of the resistance vessels, the capacitance vessels were probably engaged, since there was increased central venous pressure. The elevation of venous pressure, however, might be secondary to the reduced cardiac output and the congestive heart failure.

The absence of tachycardia could mean that the cardiac chronotropic sympathetic fibers were not activated by the lesion, implying a further dissociation of sympathetic nervous activity to blood vessels and heart. However, the absence of tachycardia could be due to other mechanisms including subsensitivity of the cardiac pacemaker resulting from heart failure or destruction of brainstem nuclei adjacent to the NTS in the parahypoglossal area, which might be necessary for the expression of changes in heart rate (26).

Paralleling the development of arterial hypertension was an immediate and marked reduction in cardiac output. The fall in cardiac output appeared to be the result of a reduction in stroke volume in response to the increase in total peripheral resistance. The decreased cardiac output was reflected in the elevated left ventricular end-diastolic pressure. The blockade of vasoconstriction with phentolamine reversed the left ventricular end-diastolic pressure to normal. The fall in cardiac output resulting from the increased afterload was further aggravated by the absence of compensatory tachycardia. Over a period of hours, cardiac output appeared to drop further as suggested by the disproportionate rate of decrease in systolic pressure and the gradual reduction of heart rate. Preterminally, the blood pressure dropped to shock...
levels without tachycardia. Whether the rapid fall in blood pressure reflected forward failure due to a sudden dilatation of peripheral vessels, possibly secondary to local acidosis, or was the result of myocardial failure remains to be determined. The rapid decline in blood pressure and presumably cardiac output preceded the terminal pulmonary edema, suggesting that the pulmonary edema was the result of left ventricular failure. An increase in circulatory volume as a consequence of vasoconstriction of the capacitance vessels or neurogenically mediated changes in the pulmonary circulation conceivably could also contribute to the pulmonary edema (31).

CENTRAL MECHANISM

The syndrome of acute neurogenic hypertension probably resulted from the release of preganglionic sympathetic neurons from the inhibition by arterial and intracardiac stretch receptors (32) and was not due to any irritative (i.e., stimulatory) effect of the lesion. The arguments in support of this conclusion are several. First, the critical site in the brainstem which had to be damaged bilaterally to produce this syndrome was the middle third of the NTS located at the obex, the so-called intermediate zone of the nucleus (11). Through this region afferent fibers from baroreceptors are funneled, and many terminate here (14). Lesions in this area abolish the reflex hypotension and bradycardia evoked by stimulation of baroreceptors or intracardiac receptors (17). Hence damage to this area of the NTS is adequate to interrupt baroreceptor input to the brain.

Second, the reflex blood pressure response to stimulation of almost all vascular stretch receptors is a fall in systemic blood pressure due to the inhibition of sympathetic outflow (33). Withdrawal of such afferent inputs by transecting the carotid sinus and the aortic depressor nerves results in a rise in blood pressure due to an increase in sympathetic activity (10). The effects of bilateral lesions of the NTS on blood pressure are thus those that would be predicted by the hypothesis that neurogenic hypertension in the rat is due to functional deafferentation of the input of vascular stretch receptors to the brain.

Third, if the hypertension were due to irritation of the NTS, then electrical stimulation of the area would also produce hypertension. Electrical stimulation of the NTS, however, produces a fall, not a rise, in blood pressure (34).

Finally, the syndrome of hypertension is qualitatively similar in most respects to that produced by sinoaortic denervation in the rat (8, 9, 35) and other species. It is neurogenic, results in increased peripheral vascular resistance, requires bilateral lesions, and is not associated with widespread activation of sympathetic fibers. Also, it is sensitive to anesthetics and decerebration. It differs from hypertension produced by sinoaortic lesions principally in its intensity. The greater magnitude of the hypertension elicited by lesions of the NTS probably relates to the fact that the central lesions interrupt depressor reflexes mediated by the vagus and by the sinoaortic nerves.

One of the most characteristic features of the hypertension evoked by NTS lesions was its dependence on the integrity of structures lying above the midbrain. Midcollicular decerebration aborted the development of hypertension before NTS lesions or abolished hypertension once NTS lesions had been established. The importance of the rostral regions of the brain in mediating the hypertension parallels the observation of Reis and Cuenod (36) and of Manning (37) that the reflex hypertension in cats elicited by sinoaortic denervation or carotid occlusion is abolished by decerebration. Our findings suggest that baroreceptors, after terminating in the medulla (11-17) engage in long-loop cardiovascular reflexes with higher brain areas. Also, they support the view that the pressor response to restoration of baroreceptor activity is subserved by neurons different from those mediating the responses to baroreceptor excitation (38). The precise localization of the rostrally situated regions necessary for the hypertension remains to be established: conceivably it lies within the hypothalamus. Baroreceptor activity projects to the hypothalamus along polysynaptic pathways (38-40), and electrical stimulation of the hypothalamus modifies baroreceptor reflexes (41, 42). Recently, Thomas and Calaresu (40) have described a restricted zone of the posterior medial hypothalamus in the cat where electrical stimulation produces hypertension and tachycardia and where unit activity can be modified by electrical stimulation of systemic baroreceptors. This critical rostral region conceivably could be a site of interaction between behaviorally determined cardiovascular events and baroreceptor reflexes.

To our knowledge the syndrome of acute fulminating neurogenic hypertension elicited by bilateral lesions of the NTS has never been described previously. Indeed, acute fulminating

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hypertension as a consequence of focal brain lesions is extremely uncommon in experimental neurology. Most reports relate to clinical cases arising from brainstem encephalitis (43–46), a relatively widespread process. However, the exquisite sensitivity of this form of hypertension to anesthesia and its dependence on the integrity of areas above the midbrain probably explains why it has not been seen before in animal studies in which the NTS has been lesioned bilaterally. However, the pulmonary edema in the unanesthetized guinea pig produced by bilateral lesions of the vagal nucleus reported by Borison and Kovacs (24), who did not measure blood pressure, possibly is similar to the syndrome we have described in this paper. The bilateral lesions of the vagal nucleus which they published also revealed damage to the NTS thereby raising the question of whether other studies in which pulmonary edema was produced by manipulation of the floor of the fourth ventricle might have also resulted from bilateral damage to the NTS (47).

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References


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