

Role of Central and Peripheral Adrenergic Mechanisms in Neurogenic Hypertension Produced by Brainstem Lesions in Rat

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ABSTRACT

Bilateral lesions of the nucleus tractus solitarius (NTS) in rats result in acute fulminating hypertension (NTS hypertension) as a consequence of central deafferentation of baroreceptors. The hypertension is due to increased peripheral resistance and decreased cardiac output. The hypertension is blocked and cardiac output is increased by phenolamine, trimethaphan (Arfonad), and reserpine but not by propranolol. In the present experiment, systemically administered 6-hydroxydopamine (6-OH-DA) did not alter NTS hypertension if the adrenal glands were intact. Adrenalectomy, however, blocked the lesion-induced rise in blood pressure in 6-OH-DA-treated rats. Intracisternally administered 6-OH-DA (600 μ g) lowered the concentration of norepinephrine only in the spinal cord and blocked the development of NTS hypertension. Local injection of 6-OH-DA into the lateral hypothalamus did not affect the hypertension. Injection of 6-OH-DA into the NTS resulted in a mild, transient elevation in blood pressure. The results of these experiments demonstrate that (1) NTS hypertension is due to increased sympathetic neural discharge, (2) during NTS hypertension sufficient adrenomedullary catecholamines are released to produce hypertension when sympathetic terminals are destroyed, (3) central noradrenergic neurons participate in the expression of NTS hypertension, and (4) baroreceptors can inhibit the release of adrenal catecholamines.

KEY WORDS blood pressure baroreceptors adrenal medulla
brain norepinephrine 6-hydroxydopamine sympathetic neurons
nucleus tractus solitarius

■ We have recently discovered that in the rat bilateral lesions of the nucleus tractus solitarius (NTS), a nucleus lying dorsolaterally in the medulla oblongata, result in the rapid development of fulminating arterial hypertension (1). It appears that this hypertension (NTS hypertension) is primarily neurogenic and results from central deafferentation of baroreceptors by destruction of their primary synapse within the brain. The consequent release of sympathetic nerve activity then produces a marked increase in peripheral resistance which leads to a reduction in cardiac output, progressive heart failure, pulmonary edema, and death.

Over the past several years increasing evidence has implicated neurons in the brain which synthesize, store, and release the catecholamine

neurotransmitter norepinephrine in the expression of some forms of hypertension (2-8). Recently, Chalmers and Reid (7) have shown that destruction of catecholamine terminals in the central nervous system by intracisternal administration of 6-hydroxydopamine (6-OH-DA) can abort that form of neurogenic hypertension produced by sinoaortic denervation. In the present study we attempted to determine if central catecholamine-producing neurons participate in the expression of hypertension produced by bilateral lesions of the NTS in the rat. We compared the effects of peripheral blockade of sympathetic nerves with the action of 6-OH-DA administered systemically, intracisternally, and intracerebrally.

Methods

The experiments were performed on male Sprague-Dawley rats (300-400 g) anesthetized with 2% halothane in 100% O₂ blown over the nose through a face mask. In acute experiments (1), a polyethylene catheter (PE50, 0.023 inches, i.d.) filled with heparinized saline (20 units/ml) was inserted into the ventral artery of the tail for direct measurement of arterial blood pressure. The catheter was fixed to soft tissue with sutures and connected to a strain-gauge transducer (Statham P23Db) for display on a polygraph (Beckman dynograph recorder 504A). Heart rate was computed

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This research was supported by Grant NS 04876 from the National Institutes of Health and by Grant NGR 33-010-179 from the National Aeronautical and Space Administration.

A preliminary report of this study has been presented at the 3rd International Catecholamine Conference, Strasbourg, May, 1973.

Please address reprint requests to Dr. Donald J. Reis.

Received July 13, 1973. Accepted for publication December 17, 1973.

Circulation Research, Vol. XXXIV, March 1974

from the blood pressure pulse wave by a cardiometer (Beckman 9858) and simultaneously displayed. At this time, in selected rats, cannulas or probes for measuring cardiac output or 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 then obtained in the quiet but awake state. The rat was then reanesthetized so that brainstem lesions could be made.

In chronic experiments, systolic blood pressure was measured by a tail cuff method (9) with a systolic auscultatory monitor that suitably amplified Korotkoff's sounds picked up by a small microphone mounted on a tail clip. Measurements were taken from rats placed in a rat holder. Each determination represented the mean of three readings.

Bilateral adrenalectomy was performed through a flank incision while the rats were anesthetized with halothane.

PRODUCTION OF HYPERTENSION BY NTS LESIONS

The methods used to produce NTS lesions have been described previously (1). In brief, the rat was placed in a stereotaxic frame with its head flexed to 45°. The region of the obex was exposed by a limited occipital craniotomy. Under direct visual observation through an operating microscope, a thin monopolar electrode consisting of a stainless steel wire (diameter 0.006 inches) coated with Teflon, bared at the tip for 0.2 mm, and carried in a no. 28 stainless steel hypodermic needle was placed into the region of the NTS by a micromanipulator. This area lies about 0.5 mm lateral to the obex and 0.4 mm beneath the ependymal surface. 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.

After surgery the wounds were closed and infiltrated with 2% procaine to minimize pain; 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 the anesthesia. At this time the rats were quiet, cardiovascular activity was reasonably stable, and, in rats with NTS lesions, hypertension was well developed. At the termination of the experiment the brain was fixed in 10% formalin for at least 2 weeks; it was subsequently sectioned to confirm the localization of the lesion (1).

MEASUREMENT OF CARDIOVASCULAR ACTIVITY

Cardiac output (CO) was measured by a thermal dilution technique described previously (1). Total peripheral resistance (TPR) was calculated from the formula: $TPR = (P_m - CVP)/CO$, where P_m is mean arterial blood pressure and CVP is central venous pressure measured in the right atrium. Mean arterial blood pressure was derived from the formula: $P_m = (P_s + 2P_d)/3$, where P_s is systolic pressure and P_d is diastolic pressure.

The significance of changes in cardiovascular and other parameters resulting from brainstem lesions was established by a paired *t*-test (10) between postlesion and prelesion measurements. For other data Student's *t*-test for independent samples was applied. A *P* value < 0.05 was considered to be significant.

DRUGS

The following drugs were used in these studies: atropine sulfate (Elkins-Sinn, Inc.), phentolamine (Regitine) (CIBA), propranolol (Sigma Chemical Co.), reserpine sulfate (Serpasil) (CIBA), and trimethaphan camsylate (Arfonad) (Roche). All stock solutions of drugs were diluted in 0.9% w/v NaCl solution before use.

6-HYDROXYDOPAMINE

6-OH-DA hydrobromide (Regis Chemical Co.) was administered systemically by a single intravenous injection of the drug dissolved in physiological saline containing 1 mg/ml of ascorbic acid as an antioxidant. The drug was injected into the femoral vein in rats briefly anesthetized with halothane. Twenty-four hours later the rats either had lesions placed in their NTS or were killed to determine the norepinephrine content of various tissues.

To examine the central effects of the drug, 6-OH-DA was injected intracisternally in rats anesthetized with halothane. The rats were placed in a stereotaxic frame with the head flexed at 45°, and the atlanto-occipital membrane was exposed. The drug was injected into the cisterna magna by a cannula made from 30-gauge stainless steel hypodermic tubing which was, in turn, mounted inside a guide cannula of 25-gauge tubing. 6-OH-DA was dissolved in a physiological salt solution containing ascorbic acid (1 mg/ml) injected over 30 seconds from a 50-μliter Hamilton syringe. The concentration of the drug was adjusted so that for each concentration of 6-OH-DA the injection volume was 10 μliters. To minimize leakage of the drug from the injection site, the cannula was left within the cisterna magna for 15 minutes. Only the ascorbic acid vehicle was administered to the controls.

Intracerebral injection of 6-OH-DA was performed by standard stereotaxic techniques with the rats anesthetized with halothane as previously described (11). A cannula similar to the one described for intracisternal administration of the drug was attached to a 50-μliter Hamilton syringe with a hand dispenser. The injection mixture consisted of 4 μliters of 6-OH-DA (4 μg/μliter as base) dissolved in ascorbic acid (0.8 μg/μliter). Controls received the vehicle alone. For intrahypothalamic administration, the drug was injected bilaterally at a posterior site (A 5.0, RL 2.0, and H 8.0 down) which corresponds to the median forebrain bundle in the lateral hypothalamus. Injection of 6-OH-DA at this site results in profound deficits in behavior and a reduction in norepinephrine and dopamine at and rostral to the site of injection (11). Because of the profound aphagia and adipsia in these rats (11), they were maintained after surgery by tube feeding with a modified diet described by Teitelbaum and Epstein (12). Injections of 6-OH-DA into the NTS were made at the same sites at which the electrolytic lesions produced hypertension.

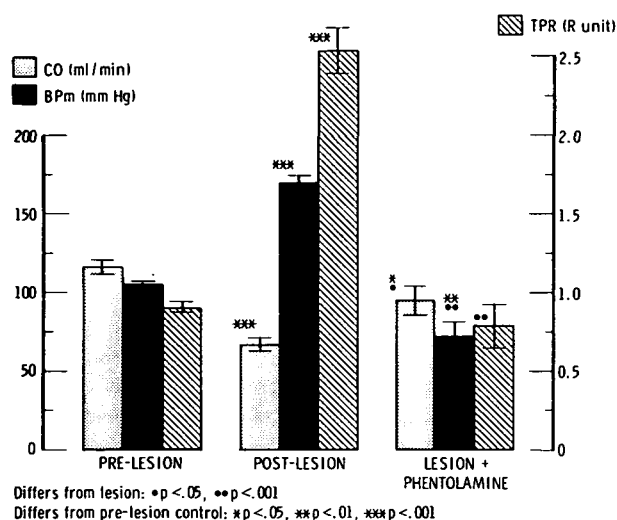


FIGURE 1

Effects of phentolamine on mean blood pressure (BPm), cardiac output (CO), and total peripheral resistance (TPR) in rats with hypertension produced by bilateral lesions of the NTS. Rats were anesthetized with 2% halothane and cannulated; the anesthesia was then discontinued and the prelesion values were obtained 30 minutes later. The rats were reanesthetized, lesions were placed in the NTS, anesthesia was discontinued, and cardiovascular activity was measured 30 minutes later (post-lesion). Phentolamine (1 mg/kg, iv) was then administered and cardiovascular activity was determined within the next 10 minutes. Note the reversal of hypertension, the decrease in total peripheral resistance, and the increase in cardiac output by the drug.

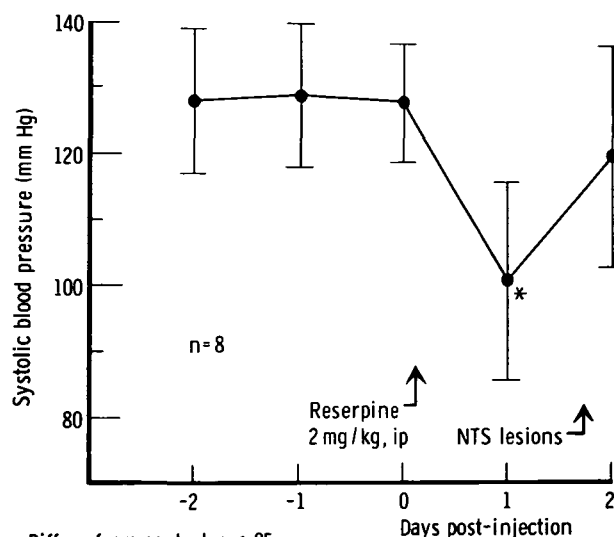
DETERMINATION OF NOREPINEPHRINE CONTENT

The regional concentration of norepinephrine in the central nervous system including the hypothalamus, the lower brainstem (pons and medulla), the cerebellum, and the spinal cord and in the heart and the spleen was measured in either unoperated controls or rats treated systemically or intracisternally with the ascorbic acid vehicle alone or with 6-OH-DA. The amines were assayed by modification of the trihydroxyindole method (13) after extraction on alumina. To evaluate the effects of systemic administration of the drug, the rats were killed by decapitation 24 hours after intravenous administration of 6-OH-DA. The brain and the spinal cord (thoracolumbar segment) were removed and regionally dissected for measurement of norepinephrine. Rats that received 6-OH-DA intracisternally were killed in the same manner 4 days later.

Results

EFFECTS OF PERIPHERAL ADRENERGIC AND GANGLIONIC BLOCKADE ON NTS HYPERTENSION

Both the α -receptor blocking agent phentolamine (1 mg/kg, iv) and the short-acting ganglionic blocking agent trimethaphan (1 mg/kg, iv) immediately reversed toward normal the ar-



* Differs from control p < .05

FIGURE 2

Effects of reserpine on arterial hypertension produced by NTS lesions. Systolic blood pressure was measured by a tail cuff method for 3 consecutive days before the injection of reserpine (2 mg/kg, ip). Reserpine produced a significant fall in blood pressure 1 day after injection. Subsequent brain lesions placed in the NTS bilaterally did not elevate blood pressure above control levels.

terial hypertension, the elevation in total peripheral resistance, and the decrease in cardiac output associated with the acute hypertension resulting from bilateral lesions of the NTS (Fig. 1). Neither drug produced any change in heart rate.

The β -receptor blocking agent propranolol (1 mg/kg, iv) partially reduced the elevated blood pressure (Table 1). The fall in blood pressure was associated with a significant ($P < 0.01$) fall in heart rate from 368 ± 10 beats/min to 280 ± 15 beats/min; this finding suggests that the decrease in blood pressure produced by propranolol is primarily a consequence of a further decrease in cardiac output. Two of six rats with NTS lesions died with pulmonary edema and acute dilation of the left ventricle shortly after the administration of propranolol; their deaths probably resulted from further compromise of the already impaired cardiac output (Fig. 1).

Development of hypertension after lesion of the NTS could also be prevented by treatment 24 hours before the lesions were established with reserpine (2 mg/kg, ip) (Fig. 2).

EFFECT OF SYSTEMICALLY ADMINISTERED 6-OH-DA ON NTS HYPERTENSION

To determine the role of peripheral noradrenergic neurons in mediating the hyperten-

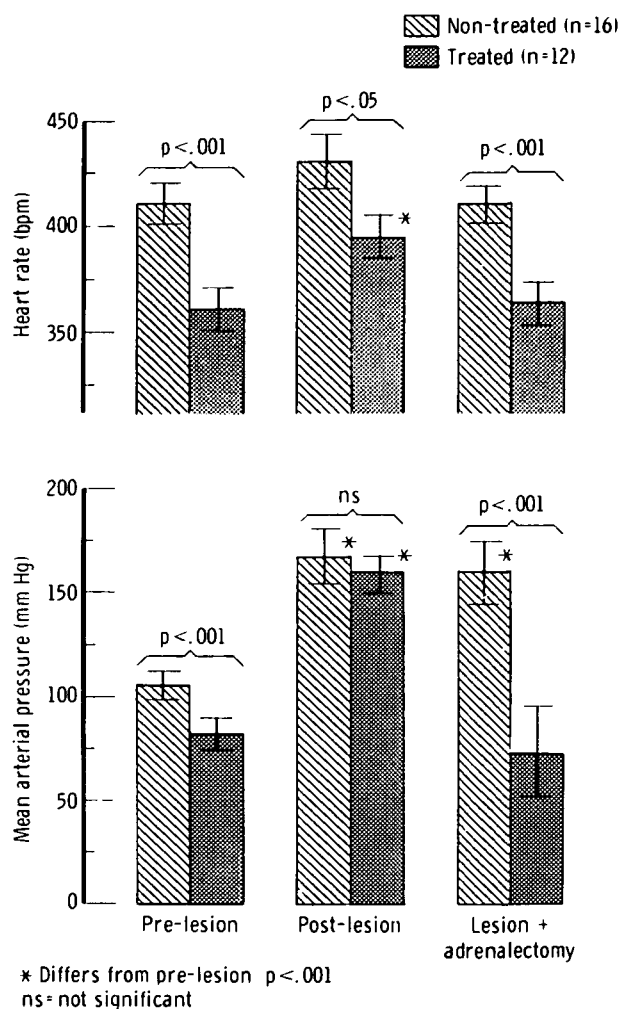


FIGURE 3

Effects of 6-OH-DA administered systemically on heart rate (top) and mean arterial blood pressure (bottom) before and after NTS lesions and adrenalectomy. Rats were treated with 6-OH-DA (100 mg/rat, iv). Twenty-four hours later the rats were anesthetized with halothane, and 30 minutes after cessation of anesthesia basal blood pressure and heart rate values were obtained before placement of lesions. Heart rate and blood pressure were directly measured from the tail artery. After measurement of heart rate and blood pressure, the rat was anesthetized with halothane (2%) and lesions were placed in the NTS. Cardiovascular activity was measured 30 minutes later. Note that 6-OH-DA significantly lowered the resting blood pressure and heart rate. Although in both treated and non-treated rats NTS lesions produced the same magnitude of elevation in blood pressure, bilateral adrenalectomy performed 30 minutes after placement of NTS lesions abolished the hypertension in treated rats.

sion produced by bilateral lesions of the NTS, the effect of 6-OH-DA (100 mg/rat, iv) administered 24 hours before surgery was examined. This dose of 6-OH-DA resulted in a significant reduction in the

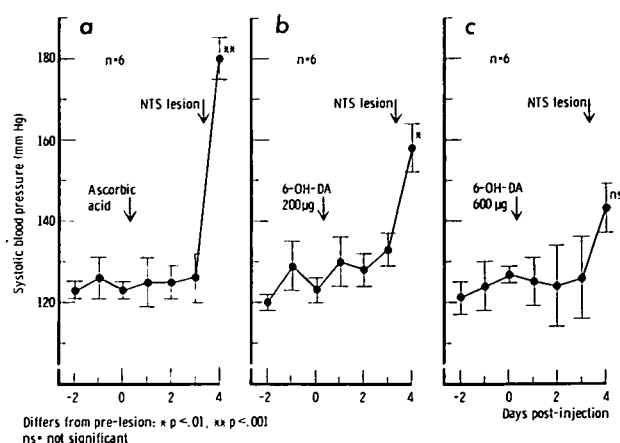


FIGURE 4

Effects of 6-OH-DA administered intracisternally on systolic blood pressure before and after NTS lesions. Blood pressure was measured by a tail cuff method for 3 consecutive days before the intracisternal injection of 6-OH-DA. Control rats (a) were treated with ascorbic acid vehicle alone. Other rats received 200 µg (b) and 600 µg (c) of 6-OH-DA in 10 µliters of ascorbic acid vehicle. Blood pressure was measured for 4 days and then bilateral lesions of the NTS were placed. Note that 6-OH-DA in the higher dose blocked and in the lower dose attenuated the NTS hypertension.

norepinephrine content in the heart and the spleen but not in the brainstem (Table 2).

6-OH-DA administered systemically produced a significant lowering of the resting blood pressure

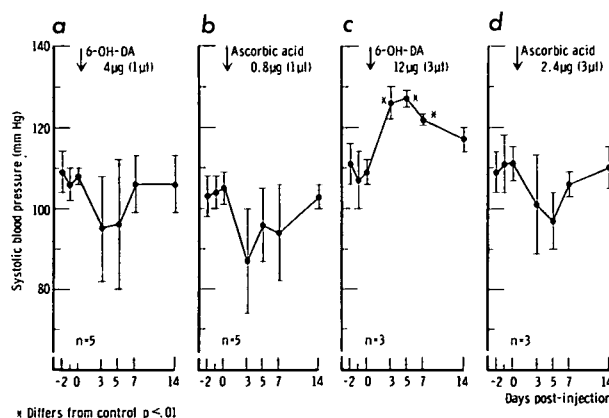


FIGURE 5

Effects on systolic blood pressure of 6-OH-DA directly microinjected into the area of the NTS. Blood pressure was measured by a tail cuff method. Blood pressure was observed for 3 consecutive days before and for 14 days after the microinjection of the drug into the NTS areas. A small dose (a) of 6-OH-DA (4 µg in 1 µl) did not produce any significant changes in blood pressure. A larger dose (c) of 6-OH-DA (12 µg in 3 µl) produced a significant rise in blood pressure which gradually returned to control levels after 14 days. Rats treated with either 1 µl (b) or 3 µl (d) of ascorbic acid vehicle alone did not show any change in blood pressure.

TABLE 1

Effects of Drugs on Hypertension Produced by Acute Lesions of the NTS in Rats

	N	Mean arterial blood pressure (mm Hg)			P
		Prelesion	Postlesion	Lesion + treatment	
Trimethaphan (1 mg/kg, iv)	6	119 ± 4	158 ± 3	102 ± 4	< 0.05
Propranolol (1 mg/kg, iv)	6	109 ± 4	162 ± 1	145 ± 9	< 0.05

Rats were anesthetized with 2% halothane and cannulated; the anesthesia was then discontinued and blood pressure was measured within 30 minutes to obtain prelesion values. The rats were then reanesthetized, lesions were placed in the NTS, and then anesthesia was discontinued. Blood pressure was measured 30 minutes later and the drugs were administered. The lesion + treatment values were obtained within 10 minutes after the administration of the drug at the time of maximal hypotensive effects. Significance ($P < 0.05$) was established by paired *t*-test comparing prelesion and postlesion blood pressure in individual rats. All values are means ± SE.

and heart rate after 24 hours (Fig. 3); this finding agreed with the observations of de Champlain and van Ameringen (9). Lesions of the NTS in 6-OH-DA-treated rats however, resulted in the development of hypertension similar in magnitude to that in rats not treated with the drug (Fig. 3 bottom). Interestingly, such lesions resulted in a small increase in heart rate in treated rats but not in untreated rats (Fig. 3 top).

The rise in blood pressure resulting from the brainstem lesions in 6-OH-DA-treated rats, but not in the controls, depended on the response of intact adrenal glands. Adrenalectomy in the 6-OH-DA-treated rats (Fig. 3) totally abolished the hypertension. This finding suggests that following the destruction of most peripheral terminals by 6-OH-DA the blood pressure may be partially maintained by the secretion of catecholamines from the adrenal medulla. This finding has been confirmed by the observations of de Champlain and van Ameringen (9). Moreover, it indicates that lesions of the NTS result, in the absence of sympathetic neurons, in a release of adrenal catecholamine sufficient to produce hypertension and possibly to increase heart rate.

EFFECTS OF INTRACISTERNAL INJECTION OF 6-OH-DA ON NTS HYPERTENSION

To determine if central catecholaminergic neurons also participate in the development of the neurogenic hypertension produced by lesions of the NTS, the effects of intracisternal administration of 6-OH-DA were examined. 6-OH-DA was injected intracisternally (600 µg/rat), and blood pressure was measured over the following 3 days. This dose of 6-OH-DA decreased the content of norepinephrine in the spinal cord but not in the hypothalamus, the cerebellum, or the brainstem (Table 3).

6-OH-DA administered intracisternally (600 µg/rat) failed to produce any change in blood pressure (Fig. 4) but did produce a significant bradycardia that was abolished by the administration of atropine (0.2 mg/kg, iv) (Table 4) as noted previously by Chalmers and Reid (7). In contrast to the drug's effects when it is administered systemically, intracisternally administered 6-OH-DA blocked the development of hypertension produced by lesions of the NTS, despite the presence of the adrenal glands. The impairment of the development of hypertension by intracisternally ad-

TABLE 2

Effects of Systemically Administered 6-OH-DA on the Content of Norepinephrine

	Norepinephrine (µg/g wet weight)		% of control	P
	Control	6-OH-DA treated		
Heart	1.175 ± 0.168 (8)	0.210 ± 0.040 (6)	17.9	< 0.001
Spleen	0.949 ± 0.110 (7)	0.358 ± 0.037 (7)	37.8	< 0.001
Brainstem	0.830 ± 0.078 (7)	0.989 ± 0.105 (7)	119	NS

6-OH-DA (100 mg/rat, iv) was administered in 0.5 ml of ascorbic acid vehicle. Twenty-four hours later the rats were killed, and the tissues were removed and assayed for norepinephrine. The number of rats tested is given in parentheses. NS = not significant.

TABLE 3

Effects of 6-OH-DA Administered Intracisternally on the Norepinephrine Content of Selected Brain Regions and the Heart

	Norepinephrine ($\mu\text{g/g}$ wet weight)		
	Control	Ascorbic acid	6-OH-DA
Hypothalamus	2.578 ± 0.109 (3)	2.428 ± 0.416 (3)	2.827 ± 0.507 (4)
Cerebellum	0.522 ± 0.096 (7)	0.640 ± 0.096 (6)	0.595 ± 0.039 (7)
Brainstem	0.830 ± 0.078 (7)	0.994 ± 0.092 (7)	0.933 ± 0.083 (6)
Spinal cord	0.942 ± 0.105 (7)	0.760 ± 0.040 (7)	$0.499 \pm 0.070^*$ (7)
Heart	1.175 ± 0.168 (8)	1.228 ± 0.150 (7)	1.149 ± 0.077 (7)

6-OH-DA (600 μg) in 10 μliters of ascorbic acid vehicle or vehicle alone were administered intracisternally. Four days later the rats were killed, and the tissues were removed for estimation of norepinephrine. Controls were killed by cervical dislocation. The number of rats studied is given in parentheses.

*Differs from control, $P < 0.01$.

ministered 6-OH-DA was dose related. Treatment with 200 $\mu\text{g}/\text{rat}$ of 6-OH-DA failed to abolish and only partially blocked the magnitude of the lesion-induced hypertension (Fig. 4).

EFFECTS OF INTRACEREBRAL INJECTION OF 6-OH-DA ON NTS HYPERTENSION

We have previously demonstrated that the development of NTS hypertension depends on the integrity of structures lying above the midbrain (1). Midcollicular decerebration prevents the development of hypertension evoked by NTS lesions or reverses the hypertension once it is established. To determine if 6-OH-DA acts to block the development of NTS hypertension by destroying catecholamine axons terminating in or passing through the hypothalamus, the drug was directly injected into the lateral hypothalamus. Since injections produce profound behavioral deficits and a significant fall in norepinephrine content in the hypothalamus and the forebrain and in dopamine content in the cau-

date nucleus (11).

Injection of 6-OH-DA into the lateral hypothalamus resulted in the development of the lateral hypothalamic syndrome of aphagia and adipsia and failed to produce any effects on blood pressure or heart rate of the control rat. It also failed to block the elevation in blood pressure produced by lesions of the NTS.

6-OH-DA (4 $\mu\text{g}/\mu\text{liter}$) was also microinjected bilaterally into the NTS. Such injections resulted 3 days later in a slight but statistically significant elevation in blood pressure which gradually returned to control levels by the fourteenth day (Fig. 5c). The effect of such an injection was not due to mechanical destruction of the tissue within the NTS since an isovolumetric injection of ascorbic acid failed to produce the effect (Fig. 5d). A smaller dose of 6-OH-DA injected into the NTS did not produce any changes in blood pressure (Fig. 5a and b).

TABLE 4

Changes in Heart Rate after Intracisternal Injection of 6-OH-DA

	N	Heart rate (beats/min)
Ascorbic acid	6	365 ± 13
6-OH-DA (200 μg)	6	376 ± 20
6-OH-DA (600 μg)	6	$280 \pm 12^*$
6-OH-DA (600 μg) + atropine	6	$390 \pm 22^\dagger$

*Differs from heart rate after administration of ascorbic acid, $P < 0.001$.

†Differs from heart rate after administration of 600 μg of 6-OH-DA, $P < 0.001$.

Discussion

The present study demonstrated again that bilateral lesions of the NTS in the rat, which centrally deafferentate baroreceptors (1, 14, 15), result in the development of a marked arterial hypertension in association with increased total peripheral resistance and decreased cardiac output. The finding that the hypertension, the increased resistance, and the decreased cardiac output can be reversed by α -receptor or ganglionic blockade further supports our views that (a) the hypertension is neurogenic and due to a marked augmentation of sympathetic nerve activity, (b) the hypertension is exclusively the result of changes in peripheral resistance, and (c) the fall in cardiac output is primarily a consequence of left ventricular overload.

Therefore, systemically administered 6-OH-DA, which destroys sympathetic nerve terminals in the heart and the spleen (9, 16, 17) and partially in the larger arteries (18) and which functionally impairs the vasoconstriction elicited by stimulation of sympathetic nerves (19, 20), should block the elevation in blood pressure produced by bilateral lesions of the NTS. (Although 6-OH-DA depletes 80–90% of the stores of norepinephrine in the heart and the spleen, Berkowitz et al. [18] have shown that comparable doses of the drug only reduce the concentrations of the amine in the aorta and the mesenteric artery of the rat to about 60% and 30%, respectively. However, although 6-OH-DA produces only partial chemical denervation of the larger vessels, the functional effects on systemic vasoconstriction may be almost complete [19, 20]. This functional effect might result because 6-OH-DA more successfully denervates smaller arterioles such as those in the spleen [21], thereby blocking vasoconstriction in the principal resistance segment of the vascular tree.) Systemically administered 6-OH-DA, however, produced a marked lowering of resting blood pressure and heart rate but did not impair the rise in blood pressure produced by NTS lesions when the adrenal glands were not removed. However, the fact that subsequent acute adrenalectomy blocked the lesion-induced elevation in blood pressure raises several interesting points. First, it adds to other evidence that 6-OH-DA administered systemically does not significantly destroy the chromaffin cells of the adrenal medulla (22, 23) and thus leaves the secretion of adrenomedullary catecholamines relatively intact. Second, this finding further supports the view of de Champlain and van Ameringen (9) that in the ab-

sence of sympathetic nerve endings, the secretion of catecholamines from the adrenal medulla is sufficient to maintain vascular tone near normal. Third, the release of catecholamines from the adrenal medulla after NTS lesions is sufficient to elevate the blood pressure to a degree comparable to that which occurs with sympathetic nerves intact.

However, since adrenalectomy in rats with intact sympathetic neurons does not attenuate the rise in blood pressure evoked by brainstem lesions (1), the present experiments suggest that 6-OH-DA-treated rats secrete more adrenomedullary catecholamines in response to NTS lesions than do rats not treated with the drug or that after treatment with 6-OH-DA adrenal catecholamines exert a more powerful action on end organs. It is not possible without direct measurement of circulating catecholamines to exclude augmented release. The latter mechanism is probable, however, because the destruction of sympathetic nerve terminals by 6-OH-DA results in a form of denervation supersensitivity as a consequence of impairment of a presynaptic form of physiological inactivation of the amines by reuptake and sequestration into storage vesicles (24, 25). The activation of the adrenal medulla in NTS hypertension parallels the increase in adrenal medullary activity that occurs in hypertension produced by treatment with deoxycorticosterone acetate (DOCA) and salt (9).

Finally, since the effect of NTS lesions is to deafferentate baroreceptors centrally (1, 14, 15), our findings suggest that baroreceptors might exert a tonic inhibition on adrenal medullary secretion. This possibility is reinforced by the observations of De Quattro et al. (26) that deafferentation of sinoaortic nerves results in an increased neurogenic drive to the adrenal medulla and also by the longstanding observations that carotid occlusion results in augmented reflex release of the adrenal catecholamines (27–30).

Our finding that 6-OH-DA administered intracisternally abolishes the lesion-induced elevation in blood pressure demonstrates that central catecholamine-producing neurons participate in the expression of NTS hypertension. The effect of 6-OH-DA on NTS hypertension is clearly through central and not peripheral mechanisms. This conclusion is supported by our findings that intracisternally, in contrast to systemically, administered 6-OH-DA (a) reduced norepinephrine within the central nervous system but not in the heart, (b) did not alter the resting blood pressure, and (c) abolished the hypertension produced by NTS le-

sions despite the presence of the adrenal glands. It is probable that central noradrenergic rather than dopaminergic neurons are necessary for the full expression of the hypertension since intrahypothalamic injections of 6-OH-DA, which damage the principal dopaminergic projections of brain (11), fail to impair the hypertension.

It is unlikely that the noradrenergic projections in the hypothalamus or the forebrain are critical in maintaining NTS hypertension, since 6-OH-DA-induced lesions effectively destroy most noradrenergic terminals within these regions (11). It is more likely, as Chalmers and Reid (7) have suggested, that a bulbospinal noradrenergic system is critical, since our injection of 6-OH-DA resulted in a significant fall in norepinephrine only in the spinal cord. The fact that intracisternally administered 6-OH-DA attenuated hypertension induced by NTS lesions further supports the studies of Chalmers and Reid (7) on neurogenic hypertension produced by sinoaortic denervation in the rabbit. These findings suggest a common engagement of central noradrenergic neurons, probably bulbospinal, in neurogenic and possibly other forms of experimental hypertension.

On the other hand, our observation that local injection of 6-OH-DA into the NTS produces a transient hypertension indicates that not all noradrenergic systems facilitate arterial blood pressure. Indeed it suggests that some systems may serve to depress arterial blood pressure. The NTS and the adjacent medial-dorsal regions of the medulla in the rat are richly innervated with noradrenergic terminals and also contain some cell bodies of noradrenergic neurons (31, 32). The role of the noradrenergic innervation of the NTS is unknown. However, recent studies (33, 34) on the pharmacological action of the centrally acting hypotensive agent lisdine, a drug that acts as an α -receptor agonist, have suggested that norepinephrine may produce its hypotensive actions by activation of baroreceptor pathways (35, 36) possibly within the NTS (36). Thus, it is conceivable that the single neurotransmitter norepinephrine may have opposing central actions on arterial blood pressure depending on the site at which it is released, the origin of the parent cell body, and, possibly, the nature of the receptor. Our findings suggest that in the NTS norepinephrine opposes a rise in blood pressure, but in the spinal cord it facilitates a rise in blood pressure.

It is unlikely that the whole syndrome of NTS hypertension can be explained exclusively on the

basis of the destruction of noradrenergic terminals in the NTS for two reasons. First, in contrast to NTS hypertension, the effect produced by microinjection of 6-OH-DA into the NTS is mild and transient. Second, NTS hypertension is similar to that produced by selective denervation of baroreceptors (1), yet baroreceptor afferents are not noradrenergic. It is more probable that the noradrenergic innervation of the NTS primarily modulates baroreceptor reflex mechanisms rather than serving as the primary activator of the reflex.

Acknowledgment

The authors wish to thank Jana Iglich for excellent technical support.

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