Regulation of Blood Pressure by Sympathetic Nerve Fibers and Adrenal Medulla in Normotensive and Hypertensive Rats

By Jacques de Champlain and Marie Reine van Ameringen

ABSTRACT

The respective roles of the sympathetic nerve fibers and adrenal medulla in the regulation of blood pressure and heart rate were studied in normotensive and hypertensive rats. Chemical sympathectomy alone, by treatment with 6-OH-DA, or bilateral adrenalectomy reduced blood pressure only slightly in normotensive animals. In animals made hypertensive with deoxycorticosterone (DOCA) and saline, each of these procedures reduced blood pressure to a greater extent than in normotensive animals, but the blood pressure remained at hypertensive levels. The combination of both procedures resulted in a greater fall in blood pressure than could have been predicted from individual effects, suggesting that the removal of one component of the sympathetic system can be compensated for by a hyperactivity of the remaining component. After chemical sympathectomy, adrenalectomy produced a rapid and marked fall in blood pressure in both normotensive and hypertensive animals and the blood pressure stabilized around 50 mm Hg within 1 hour after adrenalectomy. Since the basal blood pressure was identical in normotensive and hypertensive animals after removal of both components of the sympathetic system, this suggests that the most likely factor which would account for an elevated blood pressure in rats treated with DOCA and sodium is a synergic hyperactivity of the sympathetic fibers and adrenal medulla.

KEY WORDS 6-hydroxydopamine DOCA-and-sodium hypertension norepinephrine autonomic nervous system chemical sympathectomy adrenalectomy experimental hypertension catecholamines

Introduction

The regulation of blood pressure involves the interaction of various systems and factors (1). Hypertensive diseases could result from a variety of dysfunctions occurring at any point in this complex pressure regulatory mechanism (2). Among the various systems and factors which have been implicated in the physiopathology of various forms of hypertension, the sympathetic nervous system has been the subject of renewed interest in recent years. Our studies in animals made hypertensive with deoxycorticosterone (DOCA) and sodium have shown a hyperactivity of the sympathetic fibers and adrenal medulla (3-5) which is probably linked to variations in the sodium balance (6, 7). An increased sympathetic nervous activity could also be demonstrated by others in animals with experimental renal hypertension (8, 9) and with neurogenic hypertension (10). In spontaneously hypertensive animals, increased and decreased sympathetic tone have both been reported (11, 12).

The sympathetic nervous system has also been suspected to play a role in the pathogenesis of human hypertension, but until recently direct evidence supporting this hypothesis was lacking. Recent studies carried out under standardized conditions in unmedicated hypertensive patients with normal renal function have demonstrated increased urinary levels of
norepinephrine (13–17), vanylmandelic acid, or normetanephrine (15, 18, 19) in many patients with essential hypertension. Circulating catecholamines have also been found elevated in blood of patients with essential hypertension (20). Using tritiated norepinephrine in patients with essential hypertension, Gitlow and co-workers (21, 22) made observations consistent with an increased sympathetic activity. Although numerous studies have supported a role of the sympathetic system in experimental and human hypertension, some controversy still persists on that matter (23).

The peripheral sympathetic system is composed of sympathetic fibers and the adrenal medulla. The contribution of each of these components to the regulation of blood pressure in normotensive and hypertensive animals has not yet been clearly defined. Often studies have been made on the effects of suppressing only one of these components, and since the function of the remaining component was not evaluated, contradictory findings have been reported. For instance, investigations on the effects of immunosympathectomy and chemical sympathectomy in animals made hypertensive with DOCA and sodium have yielded opposite conclusions (24–26). The purpose of the present studies was to evaluate the respective role of the sympathetic nerve fibers and adrenal medulla on the control of blood pressure in normotensive rats and in one form of experimental hypertension. These studies have shown that there exists a functional balance between the activity of these two components in the regulation of normal cardiovascular functions and that an increased adrenergic activity might be responsible for the development and maintenance of hypertension induced by DOCA and sodium.

**Methods**

**Production of Hypertension and Recording of Blood Pressure.**—The right kidney and adrenal gland were removed from male Sprague Dawley rats weighing 80–90 g. The rats were made hypertensive by subcutaneous injections of a suspension of deoxycorticosterone pyvalate, 10 mg/week, and 1% NaCl solution to drink ad libitum for periods of 5–7 weeks (4). Both control and hypertensive animals were fed a regular laboratory diet.

The systolic blood pressure of unanesthetized animals was measured with a pulse transducer applied to the tail and recorded on a Grass model 7B polygraph (3). The blood pressure of rats anesthetized with sodium pentobarbital, 60 mg/kg, was measured by cannulation of the left carotid artery through a Statham strain gauge (Ped 23) transducer.

**Production of Chemical Sympathectomy.**—Normotensive and hypertensive rats weighing 200–300 g were given a single intravenous injection of 100 mg/kg of 6-hydroxydopamine (6-OH-DA) HC1 prepared in physiological saline containing 1 mg/ml of ascorbic acid. For study of chronic effects, the same treatment was repeated once a week.

**Adrenalectomy.**—The remaining adrenal gland was removed under sodium pentobarbital anesthesia from unilaterally adrenalectomized rats with and without hypertension and with and without sympathectomy. The arterial blood pressure and electrocardiogram were recorded for 1 hour before, and for 1 or 2 hours after, operation.

**Effect of Chemical Sympathectomy on Development of Hypertension.**—Four litters of rats were studied. Beginning at birth, two litters received weekly subcutaneous injections of 6-OH-DA, 100 mg/kg. After reaching a body weight of 100 g, all four litters were weaned and underwent unilateral nephrectomy. One litter of rats treated with 6-OH-DA and one of untreated animals were given deoxycorticosterone (DOCA) and 1% NaCl as described above for 5 weeks. The other litter of rats treated with 6-OH-DA and one of untreated rats served as controls. All animals were fed a regular laboratory diet.

**Endogenous and Tritiated Norepinephrine.**—Intact normotensive and hypertensive rats and rats adrenalectomized 8 days previously were injected in the tail vein with 25 μc of d18H-norepinephrine (New England Nuclear, 10 c/mmole) and were killed 24 hours later. All groups of animals were given 1% saline during the week preceding the experiment. Tissues were quickly removed, chilled on crushed ice, and analyzed for radioactive and endogenous norepinephrine. The tritiated norepinephrine was extracted from tissue homogenate by passage on an alumina column (27). The eluate was counted in a liquid scintillation spectrometer. Endogenous norepinephrine was isolated and assayed by modified methods of Anton and Sayre (28) and von Euler and Lishajko (29) as reported previously (3). The final values for tritiated and
endogenous norepinephrine were corrected for appropriate recovery.

Results

Acute Effects of 6-OH-DA on Arterial Blood Pressure and Heart Rate.—Immediately following one intravenous injection of 100 mg/kg of 6-OH-DA, a marked sympathomimetic effect, characterized by a rise in mean blood pressure and by an increase in heart rate, was observed in anesthetized normotensive and hypertensive rats (Fig. 1). The rise in blood pressure reached a peak in less than 5 minutes. The return of blood pressure toward initial levels was biphasic; it fell rapidly in the first 20 minutes and more slowly thereafter, reaching initial levels in about 1 hour in normotensive rats and in about 2 hours in hypertensive rats. In the following hours, the blood pressure continued to decrease and stabilized 30–40 mm Hg lower in both groups of animals. The initial heart rate was lower in hypertensive rats and the cardiac response to 6-OH-DA was less marked (Fig. 1, bottom). The heart rate of both groups of animals was 10–15% lower than the initial rates in the following hours.

![Graph](image-url)
The adrenal glands seem to contribute to the long-lasting sympathomimetic effect immediately following administration of 6-OH-DA. In adrenalectomized animals 6-OH-DA caused a rise in blood pressure of shorter duration (Fig. 2); blood pressure returned to initial levels in half the time that it took in intact animals.

**Cardiac Endogenous Norepinephrine after 6-OH-DA Treatment.**—Endogenous norepinephrine (NE) levels were measured in the heart of normotensive and hypertensive animals before and after treatment with 6-OH-DA (Fig. 3). The cardiac NE content in hypertensive rats was initially 30% lower than that of normotensive animals. Five hours after one injection of 6-OH-DA, 100 mg/kg, the endogenous NE levels were reduced by more than 90% in both groups of animals. Eight days later, however, although the cardiac NE content was still low compared to initial values, the endogenous NE levels were found significantly higher than the 5-hour values. The endogenous NE levels appeared to recover faster in hearts of hypertensive animals, being significantly higher than those of normotensive rats 8 days after 6-OH-DA treatment.

**Chronic Effects of Chemical Sympathectomy or Adrenalectomy on Blood Pressure of Unanesthetized Normotensive and Hypertensive Animals.**—Eight days after chemical sympathectomy by 6-OH-DA or after bilateral adrenalectomy, the systolic blood pressure of unanesthetized normotensive and hypertensive animals was decreased to various extents (Table 1). In normotensive animals, the fall in blood pressure was on the order of 30 mm Hg after 6-OH-DA treatment, whereas adrenalectomy lowered blood pressure only slightly (about 10 mm Hg). In the hypertensive rats, each procedure produced a fall in blood pressure of about 40 mm Hg, but the blood pressure remained at hypertensive levels after either procedure.

**Acute Effects of Adrenalectomy on Normotensive and Hypertensive Rats with and without Sympathectomy.**—To record continuously more accurate changes in blood pressure and because the measurement of blood pressure was impossible on the tail of rats subjected to both sympathectomy and adrenalectomy, the blood pressure was measured in anesthetized animals through the carotid artery. In normotensive untreated animals, adrenalectomy did not change the blood pressure significantly in the following hour (Fig. 4). However, in normotensive animals that had had sympathectomy 18 hours previously, adrenalectomy caused a marked fall in blood pressure within 5 minutes that was followed by a more gradual fall. Similar results, but of greater magnitude, occurred in hypertensive animals (Fig. 5). Adrenalectomy in untreated hypertensive rats resulted in a
progressive lowering of blood pressure of about 40 mm Hg in the following hour. In hypertensive animals treated previously with 6-OH-DA, the same procedure produced a marked fall in blood pressure within 5 minutes that, as in the normotensive rats similarly treated, continued to fall progressively in the following hour.

The effects of adrenalectomy after chemical sympathectomy seem to be due exclusively to the interruption of adrenal medullary secretion. In animals receiving adrenocortical replacement therapy by administration of cortisone acetate, 10 mg/kg, similar hypotensive effects of the same magnitude could be observed after adrenalectomy. In previously sympathectomized animals, administration of an alpha-receptor blocker (Dibenamine-HCl, 5 mg/kg) on blood pressure could mimic the effect of an acute adrenalectomy (Fig. 6). Moreover, the effects on blood pressure were rapid and reversible, as shown in studies in which the clamping and unclamping of adrenal vessels were studied (Fig. 7). The clamping of adrenal vessels caused a rapid fall in blood pressure, whereas unclamping rapidly restored the blood pressure to initial levels.

TABLE 1
Systolic Blood Pressure (mm Hg) of Unanesthetized Normotensive and Hypertensive Rats Eight Days after One Injection of 6-OH-DA or Bilateral Adrenalectomy

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>6-OH-DA</th>
<th>Adrenalectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normotensive</td>
<td>122.5 ± 1.4</td>
<td>94.0 ± 8.0*</td>
<td>111.2 ± 5.2</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>207.0 ± 2.5</td>
<td>172.0 ± 7.5†</td>
<td>165.0 ± 6.1†</td>
</tr>
</tbody>
</table>

Values are means ± se of 6–8 rats.

*P < 0.05.
†P < 0.01 vs. control values.
Acute effects of adrenalectomy on the mean arterial pressure (mm Hg) in anesthetized intact or sympathectomized normotensive animals. Each curve is the mean ±SE of 6 treated and 4 untreated animals. See text.

The effects of sympathectomy or adrenalectomy or both on mean blood pressure, systolic blood pressure, and heart rate are summarized in Figure 8 and Table 2. It should be observed that the combination of both procedures resulted in a greater fall in blood pressure than could have been predicted by adding the effects of the two procedures. It is also noteworthy that the combination of both procedures decreased the blood pressure and heart rate to identical basal levels in normotensive and hypertensive animals.

Cardiac Norepinephrine Retention in Normotensive and Hypertensive Rats before and after Adrenalectomy.—In normotensive rats, the removal of adrenal glands 8 days prior to study markedly decreased the capacity of the heart to retain tritiated norepinephrine 24 hours after intravenous injection (Fig. 9). However, endogenous norepinephrine levels of the same hearts were not modified by adrenalectomy. In hypertensive rats, the retention of tritiated norepinephrine, which...
Acute effects of adrenal clamping and unclamping in one anesthetized hypertensive animal that had been treated 1 week previously with one intravenous injection of 6-OH-DA (100 mg/kg). Short periods of clamping brought about a rapid fall in mean arterial pressure of 40 mm Hg. After opening the clamp, blood pressure was quickly restored to initial levels, and final clamping lowered it to shock levels within 1 hour.

was initially lower than that of normotensive rats, was not further decreased by removal of the adrenal glands. However, in these animals, the endogenous norepinephrine levels were significantly reduced by adrenalectomy. Whereas the specific activity of norepinephrine was markedly decreased in hearts of normotensive rats, it was increased in hearts of hypertensive rats after adrenalectomy.

Effect of Chemical Sympathectomy on the Development of Experimental Hypertension.—In 10-week-old rats, treatment with DOCA and saline for 5 weeks significantly increased the blood pressure to hypertensive levels (Fig. 10). In age-matched controls treated weekly with 6-OH-DA from birth, the blood pressure was significantly lower than that of untreated controls. In rats treated with 6-OH-DA, administration of DOCA and saline for 5 weeks failed to induce hypertension, but it did cause a rise in blood pressure from hypoten- sive to normotensive levels. The heart rate was slightly but significantly reduced only in rats treated with 6-OH-DA, whether they received DOCA and saline or not (P < 0.02).

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Effect of Adrenalectomy, Chemical Sympathectomy, or Both on Heart Rate (Beats/Min) of Anesthetized Normotensive and Hypertensive Rats</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Control</td>
</tr>
<tr>
<td>Normotensive</td>
<td>283 ± 22</td>
</tr>
<tr>
<td>Hypertensive</td>
<td>243 ± 12</td>
</tr>
</tbody>
</table>

The values are drawn from the animals illustrated in Figure 8. Each number is the mean ± se of 4-6 rats.

*P < 0.01 vs. control values.
Endogenous norepinephrine content and retention of tritiated norepinephrine in the hearts of normotensive and hypertensive animals after adrenalectomy. All groups of animals were given 1% saline to drink for the week preceding the experiment, and 24 hours before they were killed all animals were given an intravenous injection of 25 μg of [3H]norepinephrine. Each bar represents the mean ± se of 6 individual values.

Discussion

Peripheral sympathectomy was produced by administration of 6-OH-DA because that compound was found to destroy specifically the adrenergic nerve endings (30–32). It rapidly produced a marked increase in heart rate and blood pressure in normotensive and hypertensive animals because of the massive release of norepinephrine following its uptake into the nerve ending (32). The longer-lasting pressor effect observed in hypertensive animals after administration of 6-OH-DA could be explained by the supersensitivity to catecholamines reported in these animals (33–35). Catecholamines released from the adrenal medulla seem to contribute to the sympathomimetic effect, since the pressor effect was of shorter duration in adrenalectomized normotensive and hypertensive rats. These findings are in agreement with the observation that injection of 6-OH-DA into the adrenal artery caused an elevation of catecholamine secretion in the adrenal vein (36).

Treatment with 6-OH-DA produced a rapid and marked depletion of norepinephrine in hearts of normotensive and hypertensive rats. One week later, however, the endogenous norepinephrine levels had started to recover. This can be explained by the rapid regrowth of adrenergic fibers following treatment with 6-OH-DA, as was observed with the histofluorescent histochemical method (37). Although the endogenous cardiac norepinephrine was initially lower in hypertensive rats, these levels were significantly higher than those of control animals 1 week after treatment with 6-OH-DA, suggesting that the adrenergic fibers might regrow faster in hypertensive rats. In rats under observation for longer periods, the treatment with 6-OH-DA had to be repeated weekly to maintain a chronic state of sympathectomy.

In unanesthetized and anesthetized normotensive animals, the removal of adrenal glands reduced the blood pressure only slightly, whereas chemical sympathectomy reduced it about 30 mm Hg, indicating that the sympathetic fibers were more directly involved in the maintenance of blood pressure. However, removal of adrenal glands, after sympathectomy was rapidly followed by a marked fall in blood pressure, suggesting a significant compensatory role for the adrenal glands in the maintenance of cardiovascular functions after chemical sympathectomy. Identical observations were also made in dogs treated with 6-OH-DA (38). Variations in blood pressure after bilateral adrenalectomy in sympathectomized animals are most probably due to the suppression of adrenal medullary secretion. Even when corticosteroid replacement thera-
py was given to sympathectomized rats, a rapid and marked fall in blood pressure occurred after adrenalectomy. Moreover, the rapidity of changes in blood pressure is more compatible with the short action of catecholamines than with the slow and long-lasting action of cortical steroids. The clamping or unclamping of adrenal vessels in sympathectomized animals could decrease or restore the blood pressure within minutes. Finally, the observation that the hypotensive effect of adrenalectomy could be mimicked by administration of alpha-receptor blocker, strongly suggests that the changes observed after adrenalectomy in sympathectomized animals are probably exclusively related to the adrenal medulla. The possibility of a compensatory role for the adrenal medulla after chemical sympathectomy is likely, since it was previously found that treatment with 6-OH-DA does not destroy the adrenal medullary cells (32, 39, 40). Furthermore, Mueller et al. (39) have reported a marked increase in tyrosine hydroxylase activity in the adrenal medulla of animals treated with 6-OH-DA, thus suggesting an increased catecholamine synthesis rate.

In unanesthetized and anesthetized hypertensive animals, adrenalectomy or chemical sympathectomy caused a fall of blood pressure of about 40 mm Hg. After the removal of either component of the sympathetic system, the blood pressure usually remained at hypertensive levels. In sympathectomized hypertensive rats, adrenalectomy produced a greater fall in blood pressure of about 70 mm Hg, indicating that the adrenal medulla had also the capacity to compensate for and minimize the effect of sympathectomy. It is especially significant that after removal of both components of the sympathetic system, the blood pressure and heart rate fell and stabilized to identical levels (about 50 mm Hg and 180 strokes/min) in normotensive and hypertensive rats. This observation strongly suggests that the most likely factor which can account for the maintenance of an elevated blood pressure in rats treated with DOCA and sodium is a hyperactivity of both components of the sympathetic system.

The presence of both components of the sympathetic system seems to be essential for the rapid development of severe hypertension by treatment with DOCA and sodium. In our studies, chemical sympathectomy by chronic treatment with 6-OH-DA prevented the development of hypertension in rats treated with DOCA and saline for 5 weeks. However, this treatment increased the blood pressure from hypotensive to normotensive levels in sympathectomized rats, probably because of hyperactivity of the adrenal medulla. It is likely that mild hypertensive levels could have been reached if the treatment with DOCA and saline had been continued for a longer time. The findings are in agreement with those of Ayitey-Smith and Varma (24), who have shown that DOCA-and-sodium hypertension could not be induced in adequately immunosympathectomized rats. Other studies using 6-OH-DA produced opposite conclusions concerning the role of the sympathetic system on the development and maintenance of DOCA-and-sodium hypertension in the rat (25, 26). In the study of Finch and Leach (25), animals were treated with 6-OH-DA only once before starting treatment with DOCA and sodium for 11 weeks, without taking into consideration the rapid regrowth of adrenergic fibers after 6-OH-DA treatment (37). In the study of Clark et al. (26), 6-OH-DA treatment was given at 2-week intervals. This interval of treatment was probably too long to maintain a state of efficient sympathectomy, since the response to tyramine is restored to normal within this period (41) and since a significant number of fibers have regrown at that time (37). Moreover, the fact that adrenal medullectomy in combination with 6-OH-DA treatment did not prevent the development of hypertension (26) is not convincing since medullectomy itself is known to induce one type of experimental hypertension (42).

From the present study, it can be postulated in normotensive animals that there exists a functional balance between the activity of

Circulation Research, Vol XXXI, October 1972
each component of the sympathetic system in
the regulation of the cardiovascular system.
Either of these components has the ability to
compensate for a deficiency of the other
component. After chemical sympathectomy,
the adrenal medulla becomes hyperactive and
appears to liberate larger quantities of cate-
cholamines into the circulation to substitute
for the lack of neurotransmitter released at the
receptor site. On the other hand, in the
present study as well as in one other
investigation (43), bilateral adrenalectomy
causd a marked increase in norepinephrine
turnover in cardiac sympathetic fibers. This
functional relationship between adrenergic
fibers and adrenal medulla was probably
mediated through baroreceptor reflexes, since
it was found that the induction of tyrosine
hydroxylase in the adrenal medulla after
treatment with reserpine or 6-OH-DA can be
prevented by section of adrenal nerves
(44).

In hypertensive animals, both components
of the sympathetic system are hyperactive,
and this abnormality seems to be responsible
for the elevation of blood pressure. Neverthe-
less, the adrenal medulla still appears to have
the capacity to compensate for the absence of
sympathetic fibers in these animals, but, in
contrast to normotensive animals, adrenalecto-
tomy could not further increase the norepi-
nephrine turnover in cardiac sympathetic
fibers in hypertensive rats. This observation
suggests an impaired functional relationship
between the activity of both components of
the sympathetic system in this experimental
condition. However, the primary site respon-
sible for the sympathetic dysfunction in these
animals has not yet been defined. Functional
abnormalities in the sympathetic ganglion, in
the vasomotor centers of the central nervous
system, or at the site of the baroreceptors
could be responsible for the hyperactivity of
the sympathetic system. Recent studies (45)
confirmed in our laboratory (unpublished
observations) have revealed a decreased
norepinephrine turnover rate in the brain stem
of hypertensive animals. It remains to be
established, however, whether this lowering in
turnover is indicative of a primary defect at
this site or represents merely a functional
change secondary to the elevation of blood
pressure.

Acknowledgment

The authors are grateful to Miss Solange Imbeault
for her skilful technical assistance in the course of
these studies. The contribution of Mr. Andre Lacroix,
medical student, to the elaboration of these studies is
also gratefully acknowledged. Finally the advice and
criticism of Dr. Reginald Nadeau, Dr. Laurent
Descarries, and Mr. Pierre Cauhier have been most
helpful in the preparation of this paper.

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Circ Res. 1972;31:617-628
doi: 10.1161/01.RES.31.4.617

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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