Acute and Chronic Cardiovascular Effects of 6-Hydroxydopamine in Dogs

By Pierre Gauthier, Réginald Nadeau, and Jacques de Champlain

ABSTRACT

Acute and chronic cardiovascular effects of repeated injections of 6-hydroxydopamine were studied in unanesthetized dogs. The acute response to initial injections of small doses of 6-hydroxydopamine consisted of an intense sympathomimetic effect characterized by a marked increase in blood pressure and a reflex bradycardia. Three days after the administration of a total dose of 50 mg/kg of 6-hydroxydopamine, significant decreases in heart rate, blood pressure, and total peripheral resistance were observed, but cardiac output remained unchanged. The absence of a response to intravenously injected tyramine, to electrical stimulation of the right stellate ganglion, and to bilateral carotid occlusion was consistent with a state of complete peripheral sympathectomy. Along with the functional impairment of transmission at the sympathetic nerve endings, marked endogenous norepinephrine depletion was observed in the heart, carotid sinus, and spleen. In contrast, endogenous norepinephrine was increased in the stellate ganglion. The response to electrical stimulation of the distal end of the right vagus was not altered by treatment with 6-hydroxydopamine. In anesthetized dogs treated with 6-hydroxydopamine, clamping of the hilar vessels of the adrenal glands for 10 minutes caused hypotension, but the same procedure in normal dogs did not affect blood pressure, demonstrating the importance of the compensatory role of the adrenal medulla in sympathectomized animals. It is concluded that 6-hydroxydopamine can be used effectively to obtain a generalized chemical sympathectomy in unanesthetized dogs and provides a useful means for studying the role of the autonomic nervous system in the regulation of cardiovascular functions.

KEY WORDS adrenergic nerve terminals heart rate blood pressure endogenous norepinephrine tyramine right stellate ganglion stimulation adrenal glands

Sympathectomy has been frequently used to investigate the role of the sympathetic nervous system. However, surgical denervation is not specific, is usually limited to individual organs, and often requires extensive surgery and high degrees of technical skill. On the other hand, norepinephrine-depleting agents such as reserpine have a considerable number of disadvantages, because they affect other functions and mechanisms unrelated to the sympathetic nervous system. Recently, a new drug, 6-hydroxydopamine (6-OH-DA), which markedly depletes peripheral tissue stores of norepinephrine (1) and selectively destroys terminal adrenergic nerve fibers (2) has been found. The chronic effects of this agent have been studied in various species, especially rats (3–6) and cats (7, 8), but only to a limited extent in dogs (9).

The present paper describes the acute and the chronic effects of 6-OH-DA administered intravenously in unanesthetized dogs. The responses to intravenously administered tyramine in conscious dogs and to direct or reflex sympathetic nerve stimulation in anesthetized
dogs were used to test the effectiveness of the chemical sympathectomy. The relative roles of peripheral sympathetic innervation and adrenal medullary secretion in the control of blood pressure were also evaluated in these dogs.

**Methods**

**SURGICAL PROCEDURES**

Adult mongrel dogs (4–8 kg) of either sex were prepared under sodium pentobarbital anesthesia (30 mg/kg, iv). The right external jugular vein and the left carotid artery were exposed. A Teflon catheter was threaded through the left carotid artery into the descending aorta. A catheter of the same type was placed in the right external jugular vein. The catheters were sutured to surrounding tissues and exteriorized through the skin at the back of the neck. Streptomycin (Pfizer) (15–20 mg/kg, im) was given after surgery and repeated daily thereafter. Both catheters were flushed daily with small amounts of heparin sodium.

Two days after surgery, the dogs were trained to lie quietly unrestrained on a table while they were connected to the recording apparatus. A peripheral-lead electrocardiogram was obtained from two electrodes fixed on the forelimbs. The arterial blood pressure was monitored by a Statham Pd 23 transducer from the catheter previously inserted into the aorta through the carotid artery. Electrocardiographic and blood pressure tracings were recorded simultaneously on a direct-writing Grass polygraph. After 1 or 2 days of training, a stable hemodynamic state was obtained at which time control values were calculated. Cardiac output was measured by the dye-dilution technique on three consecutive days before and after treatment with 6-OH-DA. Total peripheral resistance was calculated by dividing mean blood pressure (mm Hg) by cardiac output (liters/min). The responsiveness of the preparation to an intravenous injection of tyramine (100 μg/kg) was determined before and after administration of 6-OH-DA.

**ADMINISTRATION OF 6-HYDROXYDOPAMINE**

After the initial control period of 3 days, unanesthetized dogs were injected intravenously with a total dose of 50 mg/kg of 6-OH-DA (Kitsner Labjant, Goteborg, Sweden). Since 6-OH-DA produces a strong sympathomimetic effect, fractionated doses were administered over a period of 10 hours. The initial dose given was either 0.5 or 1.0 mg/kg followed, after the return to initial blood pressure and heart rate values, by increasing doses of 2, 3, 4, and 5 mg/kg until a cumulative dose of 15 mg/kg had been reached. The last 35 mg/kg was given in two doses of 10 mg/kg and one of 15 mg/kg. The hematocrit was measured before and at 10-minute intervals after each administration of 6-OH-DA. When hematocrit occurred, a solution of 5% dextran was infused intravenously to restore the plasma volume and to decrease the hematocrit towards its normal value.

All the injections in conscious dogs were made with a hand-driven syringe in 1-ml volumes. The jugular catheter was washed with 3 ml of saline immediately after the injection. The solution of 6-OH-DA was prepared immediately before injection by dissolving the drug in physiologic saline containing ascorbic acid (1 mg/ml). In all cases, heart rate, blood pressure, and hematocrit were permitted to return to initial levels before the following injection was made, and a minimum period of 30 minutes was allowed between two successive injections.

**DIRECT AND REFLEX NERVE STIMULATION**

A group of five control dogs and a group of five dogs that had been treated with 6-OH-DA 5 days previously were anesthetized with sodium pentobarbital (30 mg/kg, iv). After tracheal intubation, the dogs were placed on assisted respiration with a Harvard pump. The chest was opened at the level of the fourth right intercostal space. The right stellate ganglion was exposed and prepared for stimulation with bipolar silver electrodes. Square-wave stimuli of 2 msec in duration and of supramaximal voltage were delivered for 15 seconds from a Grass S4 stimulator at frequencies of 1, 3, 10, and 30 cps. The right and left vagus nerves were exposed and severed in the neck. The distal end of the right vagus was stimulated as described for the right stellate ganglion. The pressor and heart rate responses to acute carotid occlusion (1 minute) were also studied in these dogs.

**CLAMPING OF THE ADRENAL VESSELS**

In two other control and treated groups of five dogs each, a midline abdominal incision was made and the adrenal glands and surrounding vessels were dissected. Smooth clamps were placed on the hilar vessels of the glands for 10 minutes (adrenal clamping) to temporarily eliminate the influence of adrenal medullary secretion on resting blood pressure. Mean blood pressure was recorded. Control values were recorded during a 5-minute period before adrenal clamping.

**ENDOGENOUS NOREPINEPHRINE**

Endogenous norepinephrine content was determined on the following samples of tissue: heart (sinus node, right atrial appendage, left ventricular wall, and left ventricular apex), right carotid sinus, left stellate ganglion, and spleen. At the time of sampling, tissue fragments were quickly
Electrocardiographic (lead aVp) and aortic blood pressure tracings showing the acute effect of 0.5 mg/kg of 6-OH-DA intravenously administered in an unanesthetized dog. Time indicated is seconds after injection. A hypertensive response developed rapidly after the injection and reached its maximum at 145 seconds. A reflex bradycardia, characterized by the emergence of a slow nodal rhythm, appeared concomitantly with the blood pressure rise. Ventricular ectopic beats were usually observed during the maximal blood pressure response (145 seconds).

The statistical significance of the difference between various results was estimated by variance analysis.

Results

ACUTE CARDIOVASCULAR EFFECTS OF 6-HYDROXYDOPAMINE

The intravenous administration of small doses of 6-OH-DA (0.5 or 1.0 mg/kg) was followed immediately by an intense sympathomimetic response characterized primarily by a marked increase in blood pressure and a reflex bradycardia (Fig. 1). Initial injections of 0.5 mg/kg of 6-OH-DA caused an increase of 148 ± 18 mm Hg in the mean arterial blood pressure. In 8 of 14 dogs, a different response was observed when a cumulative dose level of 3–5 mg/kg was reached. Following the initial reflex bradycardia, a slowly developing cardiac acceleration appeared, reaching its maximum up to 1 hour after the injection. The maximal heart rate observed was in the range of 180 to 230 beats/min. Tracings recorded during the development of this cardiac acceleration revealed that the normal respiratory arrhythmia had progressively disappeared, leading to a steady uninterrupted rapid heart rate.

Tachyphylaxis developed rapidly during the consecutive administration of progressively increasing doses of 6-OH-DA. As shown in Figure 2, the initial injection of 6-OH-DA caused a maximal blood pressure response which lasted for about 45–60 minutes. The blood pressure rise in response to subsequent higher doses of 6-OH-DA was markedly decreased compared to the initial response. At a cumulative dose level of 10 mg/kg of 6-OH-DA, the increment of blood pressure rise was only 20–30% of the initial response (Fig. 2) and the effect lasted for about 10–20 minutes. The successive blood pressure responses to higher doses of 6-OH-DA were of similar magnitude.

Each intravenous injection of 6-OH-DA caused a degree of hemoconcentration which could be correlated with the height of the blood pressure response. The bottom part of
Tachyphylactic effect of serial injections of 6-OH-DA on the blood pressure response. A total dose of 50 mg/kg was injected in fractionated, increasing doses. Changes in blood pressure are expressed in percent of the maximal response, which was obtained with the first injection. The blood pressure response markedly decreased following the three initial injections. After a cumulative dose of 10 mg/kg was reached (fourth injection), the blood pressure rise was about 20–30% of the initial response and remained constant during the following injections of even greater doses of 6-OH-DA. Each point represents the mean percent rise ± se for five dogs. Numbers under each point are the mean control blood pressure before each injection.

Figure 3 illustrates that following the three first injections of 6-OH-DA the hematocrit increased from a control value of 35% to more than 50%. As the blood pressure responses diminished with successive injections of 6-OH-DA, the changes in hematocrit were less marked. It was also observed that without an adequate and immediate replacement of plasma volume by exogenous fluids, the dogs died in shock within a few hours. In 14 experiments carried out in unanesthetized dogs, the maximum increase in hematocrit, after correction with exogenous fluids, averaged 8.5%. This

| TABLE 1 |

Cardiovascular Changes following Treatment with 6-Hydroxydopamine

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>72 hours after 6-OH-DA</th>
<th>Change from control (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>99.2 ± 3.9</td>
<td>81.6 ± 3.4†</td>
<td>-17.7</td>
</tr>
<tr>
<td>Blood pressure (mm Hg)</td>
<td>99.5 ± 6.8</td>
<td>81.6 ± 2.4†</td>
<td>-17.9</td>
</tr>
<tr>
<td>Cardiac output (liters/min)</td>
<td>1.619 ± 0.1</td>
<td>1.713 ± 0.1</td>
<td>+ 5.8</td>
</tr>
<tr>
<td>Stroke volume (ml/stroke)</td>
<td>16.37 ± 0.7</td>
<td>20.8 ± 1.3†</td>
<td>+27.3</td>
</tr>
<tr>
<td>Peripheral resistance (mm Hg/liters/min)</td>
<td>61.4 ± 4.3</td>
<td>48.9 ± 5.7</td>
<td>-20.4</td>
</tr>
</tbody>
</table>

Values are means ± se for three dogs.
*50 mg/kg injected intravenously.
†P < 0.01 compared to control.
‡P < 0.05 compared to control.
maximum effect was obtained during the injection of the first cumulative dose of 5 mg/kg.

**CHRONIC CARDIOVASCULAR EFFECTS OF 6-HYDROXYDOPAMINE**

Control heart rate and mean arterial blood pressure values were 98 ± 3 beats/min and 96 ± 4 mm Hg respectively, in 10 unanesthetized dogs at rest. Three days after the administration of 50 mg/kg of 6-OH-DA, the heart rate and the mean blood pressure averaged 84 ± 3 beats/min and 82 ± 2 mm Hg respectively. The cardiac output remained unchanged, but the peripheral vascular resistance was 20.4% lower and the stroke volume was 27.3% higher than their respective control values in 3 dogs studied before and after 6-OH-DA treatment (Table 1). Out of a total of 14 dogs, 3 dogs seemed unable to maintain a normal upright posture on all four limbs for more than 5 seconds during the first 3 days following 6-OH-DA treatment. A fall in blood pressure from 80 to 40 mm Hg was documented in 1 dog as it assumed a standing position.

**NOREPINEPHRINE CONTENT**

The norepinephrine content in various organs 5 days after treatment with 6-OH-DA is detailed in Table 2. Tissue samples from the right atrium, sinus node region, and apex of the left ventricle were found to be depleted of their endogenous norepinephrine by more than 97%. In the left ventricular wall at the base, the endogenous norepinephrine was reduced by about 90%. The norepinephrine content was also markedly reduced in the carotid sinus and in the spleen. In contrast, the norepinephrine content was significantly increased by about 10% in the stellate ganglion after 6-OH-DA treatment.

**RESPONSE TO INTRAVENOUSLY ADMINISTERED TYRAMINE**

The response to tyramine (100 μg/kg) injected intravenously in unanesthetized dogs was completely abolished 48 hours after 6-OH-DA treatment. Although as much as four times the dose used in control dogs was injected, only slight effects on blood pressure and heart rate were observed in the dogs treated with 6-OH-DA (Fig. 4).

**RESPONSE TO DIRECT AND REFLEX AUTONOMIC NERVE STIMULATION**

The chronotropic response to stimulation of the right stellate ganglion was studied in anesthetized vagotomized dogs 5 days after 6-OH-DA treatment. Figure 5 shows that stimulation at frequencies of 1-30 cps for periods of 15 seconds did not change the heart rate of the dogs treated with 6-OH-DA. Increasing the voltage of stimulation up to 15 v did not initiate a response. In the control group of dogs, a clear chronotropic response was observed during sympathetic nerve stimulation at all frequencies studied. In contrast to the abolished response to sympathetic nerve stimulation, the response to stimulation of the distal end of the right vagus nerve was

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**TABLE 2**

<table>
<thead>
<tr>
<th>Endogenous Norepinephrine (μg/g tissue) in Normal Dogs and Dogs Treated with 6-Hydroxydopamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Sinus node</strong></td>
</tr>
<tr>
<td>Control                                      2.780 ± 0.400                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      0.063 ± 0.019                                  8</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Right atrium</strong></td>
</tr>
<tr>
<td>Control                                      2.507 ± 0.384                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      0.053 ± 0.018                                  8</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Base of left ventricle</strong></td>
</tr>
<tr>
<td>Control                                      0.625 ± 0.058                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      0.008 ± 0.009                                  8</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Apex of left ventricle</strong></td>
</tr>
<tr>
<td>Control                                      0.633 ± 0.111                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      0.017 ± 0.003                                  8</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Right carotid sinus</strong></td>
</tr>
<tr>
<td>Control                                      3.145 ± 1.117                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      0.338 ± 0.116                                  8</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td><strong>Left stellate ganglion</strong></td>
</tr>
<tr>
<td>Control                                      6.395 ± 1.075                                  8</td>
</tr>
<tr>
<td>6-OH-DA*                                      1.290 ± 0.457                                  7</td>
</tr>
</tbody>
</table>

Values are means ± SE. N = number of dogs tested.

*50 mg/kg intravenously administered.
†P < 0.01 compared to control values.
‡P < 0.05 compared to control values.
Intravenously injected tyramine in normal unanesthetized dogs caused an increase in blood pressure (top) and a reflex decrease in heart rate (bottom). This response was abolished 2 days after treatment with 6-OH-DA (50 mg/kg). Even when four times the dose used in control dogs was injected (400 μg/kg), only slight effects on blood pressure and heart rate were observed in the dogs treated with 6-OH-DA. The cardiovascular responses to tyramine were determined in five normal and in five dogs treated with 6-OH-DA. The responses are expressed as the changes from the initial values ± SE.

unchanged in dogs treated with 6-OH-DA compared to that in control dogs (Fig. 6).

Bilateral carotid occlusion for 1 minute caused an increase in mean arterial blood pressure of 40 ± 8 mm Hg and an acceleration in heart rate of 18 ± 8 beats/min (Fig. 7) in the control dogs. After 6-OH-DA treatment, the pressor and chronotropic responses to carotid occlusion were almost completely abolished.

EFFECT OF CLAMPING OF ADRENAL VESSELS ON BLOOD PRESSURE

The effect of adrenal clamping for a period of 10 minutes was studied under sodium pentobarbital anesthesia in control dogs and in dogs treated with 6-OH-DA. These experiments demonstrated the importance of adrenal medullary secretion in the maintenance of blood pressure after treatment with 6-OH-DA. Bilateral clamping of all the main vessels supplying both adrenal glands for 10 minutes caused no significant change in arterial blood pressure in normal dogs (Fig. 8). The removal of the clamps resulted in a marked increase in blood pressure (from 105 ± 5 mm Hg to 211 ± 8 mm Hg) which returned towards initial values within about 8 minutes. In the dogs treated with 6-OH-DA, the initial blood pressure was lower than it was in normal dogs (70 ± 5 mm Hg). In the first 10 minutes after clamping, the blood pressure fell progressively to about 36 ± 3 mm Hg. Unclamping the adrenal vessels resulted in a marked increase in blood pressure (206 ± 3 mm Hg), as it did
6-HYDROXYDOPAMINE IN DOGS

**FIGURE 6**

Negative chronotropic effect of electrical stimulation of the distal end of the right vagus nerve in normal dogs and in dogs treated with 6-OH-DA (50 mg/kg). Top: The minimal heart rate obtained during vagal stimulation is given for both groups of dogs. There was no difference between the response of both groups of dogs at 8, 16, and 32 cps. On the other hand, a significant difference was observed at 4 cps, which may be related to a difference in the initial heart rate (at 0 cps). Bottom: No significant differences were observed when the response was calculated as percent of control heart rate. Each curve is the mean for five dogs. Vertical bars indicate the se.

**FIGURE 7**

Blood pressure and heart rate responses to bilateral carotid occlusion (1 minute) in five normal dogs and five dogs treated with 6-OH-DA (50 mg/kg). Numbers on the ordinate refer to changes in mean arterial blood pressure and heart rate in mm Hg and beats/min ± se. Carotid occlusion produced an increase in blood pressure and heart rate in normal dogs. Five days after 6-OH-DA treatment, these responses were almost completely abolished.

Noncardiovascular Effects of 6-Hydroxydopamine

During the serial injections of 6-OH-DA, piloerection appeared in all dogs after a cumulative dose of 2-5 mg/kg of 6-OH-DA had been reached and disappeared before the total dose of 50 mg/kg had been completed. During the course of injections, mydriasis and a profuse salivation were also noted. Vomiting occasionally occurred following 6-OH-DA administration. This effect appeared most of the time 2-4 minutes after an injection but could not be associated with a given dose of 6-OH-DA. Diarrhea appeared within 12 hours after the beginning of the injections of 6-OH-DA. Miosis and relaxed nictitating membranes were noted in all dogs when they were examined in the days following 6-OH-DA treatment.

**Discussion**

Previous studies in various species, especially in cats (7, 8) and rats (3-6), have shown that 6-OH-DA, injected in sufficiently high doses, produced an effective chemical sympathectomy. However, there exists no study on the effects of 6-OH-DA in dogs except that of Stone et al. (9) who injected low doses of 6-OH-DA in anesthetized dogs. The present study describes the acute and the chronic effects of 6-OH-DA intravenously administered in fractionated doses in unanesthetized
Effect of adrenal clamping on resting blood pressure in normal dogs and dogs treated with 6-OH-DA (50 mg/kg). In normal dogs, clamping all the main vessels of the adrenal glands caused no change in arterial blood pressure. The same procedure in the dogs treated with 6-OH-DA resulted in a rapid fall in mean arterial blood pressure. The removal of the clamps produced a marked increase in blood pressure in both groups. The return to initial values occurred later in the dogs treated with 6-OH-DA than in the control dogs. Each curve is the mean arterial blood pressure response ± se for five dogs.

This constitutes a new method of obtaining an effective sympathectomy in the dog, an animal extensively used in studies of cardiovascular functions.

The initial injections of 6-OH-DA produced an intense adrenergic response characterized by a marked rise in blood pressure, piloerection, mydriasis, and a profuse salivation. An acute hypertensive response has been reported by other investigators in anesthetized rats and dogs following the intravenous injection of small doses of 6-OH-DA (6, 9). It has been proposed that this response results mainly from the massive displacement by 6-OH-DA of norepinephrine from its binding sites in adrenergic nerve endings (6), as suggested initially by Porter et al. (12) in 1965 and later by Thoenen and Tranzer (13) in 1968. It has been shown that 6-OH-DA must enter into the nerve endings to produce its sympathomimetic and depleting effects (5, 14).

Tachyphylaxis developed rapidly as increasing amounts of the drug were injected. This phenomenon was also observed by Varagic and Kazic (6) in anesthetized rats. After a cumulative dose of 10 mg/kg of 6-OH-DA had been reached by repeated injections, the magnitude of the blood pressure changes following additional injections of larger doses became relatively constant and represented only 20–30% of the initial response. This may indicate that, after reaching this dose level, the sympathetic fibers were depleted of their norepinephrine and that the remaining pressor response could be secondary to the liberation of catecholamines from the adrenal medulla or due to a direct action of the drug on alpha receptors.

The important hemoconcentration observed during the acute pressor action of 6-OH-DA may have resulted either from an increased number of circulating erythrocytes due to spleen contraction, as has been seen during injection of other pressor substances (15), or to a reduction of plasma volume possibly attributable to the increased amount of circulating catecholamines released by 6-OH-DA. It has been previously reported that a
prolonged infusion of norepinephrine in man (16) and dog (17) produces an increase in hematocrit and a decrease in plasma volume. This latter possibility is most likely since dogs whose plasma volume was not corrected by the administration of dextran died in a state of shock shortly after the acute effect.

A tachycardia of long duration has been previously reported following the intravenous injection of 6-OH-DA in anesthetized kittens (8), dogs (9), and rats (5, 6). In the present experiments in unanesthetized dogs, a reflex bradycardia was observed in response to baroreceptor activation by the marked increase in blood pressure. The tachycardia reported in anesthetized animals may be explained by the well-known parasympatholytic effect of anesthetic agents which prevents the appearance of a reflex bradycardia (18–20). The observation of a cardiac acceleration in about 50% of the unanesthetized dogs after a cumulative dose of 3–5 mg/kg of 6-OH-DA remains unexplained.

6-OH-DA caused a marked depletion of endogenous stores of norepinephrine in various portions of the heart, spleen, and carotid sinus. The depletion of norepinephrine was greatest in the sinus node area, the right atrium, and the apex of the left ventricle. The remaining norepinephrine (about 2%) does not indicate that a proportional amount of adrenergic fibers remain in the tissue. In studies made in rats after 6-OH-DA treatment, it was reported that no adrenergic nerve endings could be observed in the heart when 5% of the initial norepinephrine content was still detectable (3). Part of the remaining norepinephrine can be localized within preterminal fibers which are not completely destroyed by 6-OH-DA treatment (21). The difference in the degree of depletion among various organs or within various portions of one organ may be explained by the difference in the fractional blood flow irrigating these tissues (13, 22).

The norepinephrine content of the stellate ganglion was increased after sympathectomy in dogs. The lack of norepinephrine depletion in this tissue is consistent with findings in rats and cats that 6-OH-DA produces a complete degeneration of terminal adrenergic nerve fibers without destroying the cell bodies (2, 3). The increase of about 70% in the catecholamine content of the stellate ganglion may be explained by impaired axonal flow after destruction of the terminal portion of the nerve fiber, as has been shown after nerve ligation by Dahlstrom (23). An increase in norepinephrine synthesis, mediated by an enhanced sympathetic reflex activity in response to impairment of postganglionic sympathetic transmission, has been shown to occur in the adrenal medulla after 6-OH-DA administration (24). This mechanism, however, cannot be invoked to explain the present findings, since Thoenen (25) has recently observed that tyrosine hydroxylase was unchanged in sympathetic ganglia after treatment with 6-OH-DA.

In the days following 6-OH-DA treatment, functional impairment of transmission at the sympathetic nerve endings was demonstrated in five dogs by direct, indirect, and reflex stimulation of the sympathetic nervous system. The reduced response to carotid occlusion after 6-OH-DA treatment is in agreement with observations in dogs after surgical sympathectomy (26). The lack of response to intravenous tyramine and to electrical stimulation of the stellate ganglion also supports the concept of a complete sympathetic denervation in these dogs. This is corroborated by the appearance of noncardiovascular signs of sympathetic denervation such as miosis, relaxed nictitating membranes, and diarrhea. Moreover, the normal parasympathetic response following vagal electrical stimulation in dogs treated with 6-OH-DA demonstrates the specificity of chemical sympathectomy.

The chemical sympathectomy by 6-OH-DA resulted in a lowering of the mean arterial blood pressure and mean heart rate in resting unanesthetized dogs by about 15–20%. This suggests that in normal dogs the sympathetic nervous system plays a tonic role in maintaining blood pressure and heart rate at their resting levels. Similar results have been reported in unanesthetized rats after chemical sympathectomy (5, 27). These findings are
also consistent with those reported in unanesthetized dogs after surgical sympathectomy (26, 28). It has been suggested previously that following sympathetic denervation the cardiac output is an important determinant of mean aortic pressure (29). The fact that cardiac output was maintained at normal levels in our experiments suggested that the slight fall in blood pressure following chemical sympathectomy was mainly the result of diminished peripheral vascular resistance rather than the result of a fall in cardiac output. The maintenance of a normal cardiac output after 6-OH-DA treatment resulted from a decrease in heart rate and an increase in stroke volume. This latter observation may indicate that the heart obeys Starling's law after chemical sympathectomy, as has been already suggested in conscious dogs with surgically denervated hearts (30).

The importance of the compensatory role of the adrenal medulla in sympathetecmized dogs has been demonstrated in the present study. Only a slight fall in blood pressure (17%) was observed in conscious dogs on the days following 6-OH-DA treatment. In normal anesthetized dogs, adrenal clamping for 10 minutes caused relatively no change in the mean blood pressure, but the same procedure in the chemically sympathectomized dogs resulted in a marked fall in blood pressure. Similar results were reported recently in rats (5). The adrenal medulla, already known to be hyperactive in sympathetecmized animals (31), appears to compensate and to minimize the effect of chemical sympathectomy on blood pressure by increasing the rate of catecholamine secretion into the circulation. The rate of synthesis of adrenal catecholamine was increased in the adrenal glands of rats 40 hours after 6-OH-DA treatment (31). The almost total destruction of peripheral sympathetic fibers and the increased capacity of the adrenal medulla to synthesize catecholamines would suggest that this latter organ could supply the peripheral adrenergic receptors with the depleted neurotransmitter. In addition, the physiological effects of catecholamines released from the adrenal medulla are increased, since chemical sympathectomy leads to presynaptic supersensitivity (4, 7, 32).

As proposed previously (5), the present experiments suggest a synergic relationship between the peripheral sympathetic nervous system and the adrenal medulla in the tonic maintenance of normal blood pressure.

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