Sensitization of Arteries, Veins, and Small Vessels to Norepinephrine After Cocaine

By Francois M. Abboud, M.D., John W. Eckstein, M.D., Ben G. Zimmerman, Ph.D., and Michael H. Graham, B.Sc.

Cocaine augments the pressor effect of norepinephrine in dogs. It is not known whether this greater pressor effect is caused by a greater cardiac output or greater vascular resistance or both. Macmillan's observations on the perfused ear of rabbit suggest that norepinephrine causes a greater increase in vascular resistance after cocaine. The effect of norepinephrine on veins, arteries, and small vessels after cocaine has not been reported. Veins, arteries, and small vessels interpose independent resistances which contribute in varying degrees to total resistance. It is possible that a greater increase in total resistance to blood flow in response to the catecholamine may be caused by greater constriction of only one of the vascular segments. If such selective sensitization occurred after cocaine it might have important physiologic and pharmacologic implications.

The present experiments were done to measure vascular responses to norepinephrine after cocaine and to determine whether changes in responses of veins, arteries, and small vessels in the perfused foreleg of dog were similar.

Methods

Twenty-nine male mongrel dogs (15 to 20 kg) were studied. They were anesthetized either with pentobarbital sodium (30 mg/kg) or a mixture of chloralose (50 mg/kg) and urethane (500 mg/kg). They were given decamethonium bromide (0.3 mg/kg) intravenously, and ventilated artificially through a cuffed endotracheal tube connected to a fixed-volume respiratory pump. With the animals lying on their sides the left brachial artery and vein and the median, radial, ulnar and musculocutaneous nerves were exposed high in the foreleg. A superficial dorsal metacarpal vein and a superficial volar metacarpal artery were exposed through 0.5 cm incisions in the forepaw and cannulated using a technique similar to that described by Haddy et al. The metacarpal vein was ligated and incised upstream from the ligature. A small polyethylene tube (PE10, 0.6 mm O.D.) was manipulated peripherally through the incision and past valves until its tip lay in a position from which blood could be aspirated and saline infused freely causing a rapid rise and fall in small vein pressure. In this position the tip lay in the web between the toes and small rhythmic pressure oscillations, which were synchronous with pressure changes in the brachial vein, were recorded. The tube was tied in place. The superficial volar metacarpal artery was ligated and an incision was made downstream from the ligature. A small glass tube (0.5 mm O.D.) with a polished tip was advanced into the artery peripherally about 1 or 2 cm.

Following intravenous injections of heparin sodium (5 mg/kg) the brachial artery was ligated and incised. The peripheral segment was cannulated and the foreleg was perfused with blood from the right femoral artery with a Sigmamotor pump. The output of the pump was pulsatile and independent of systemic arterial pressure over the range encountered. Flow was adjusted initially so that perfusion pressure was approximately the same as systemic arterial pressure. This flow was maintained constant throughout the experiment. The flow rates ranged from 52 to 105 ml/min and averaged 70 ml/min. Pressures in the perfused brachial artery, the brachial vein, the small artery and small vein in the forepaw, and the left
femoral artery were measured with Statham transducers and recorded continuously with a Sanborn direct-writing oscillograph. Transducers having a volume displacement of 0.01 mm³/100 mm Hg (model P23 Gb) were used for pressure measurements in small vessels.

Two or three doses of l-norepinephrine bitartrate, angiotensin II,* serotonin creatinine sulfate, and tyramine sulfate were injected into the tubing of the pump close to the brachial artery before and after intravenous administration of 0.5, 5 or 10 mg/kg of cocaine hydrochloride. In each experiment the responses to norepinephrine and one of the three other drugs (angiotensin, serotonin or tyramine) were tested before and after one dose of cocaine. The doses are recorded in table 1. The effects of sympathetic nerve stimulation on blood vessels in the perfused foreleg were tested also before and after 5 mg/kg of cocaine. The left stellate ganglion was exposed through an incision made in the left first intercostal space. Electrodes were applied around the large gray ramus communicans to C7 extending from the cephalic pole of the ganglion. This nerve was stimulated twice before and twice after cocaine. Stimulations were made at 3 to 12 volts with a frequency of 20 cycles/sec, each cycle lasting 2 msec, for a total period of one minute.

The vasoactive drugs and the nerve stimulations caused large changes in pressure in the perfused foreleg but had negligible systemic effects. The exposed median, ulnar, radial, and musculocutaneous nerves were sectioned in dogs in which the sympathetic nerves were not stimulated. Ligatures were tightened around the muscle groups high in the foreleg to obliterate the collateral circulation in animals which received the intra-arterial infusions of norepinephrine.

Norepinephrine was dissolved in 5% glucose in water. Other drugs were in 0.9% solution of sodium chloride. The volumes injected varied from

<table>
<thead>
<tr>
<th>TABLE 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Changes in Resistance of Vascular Segments in the Foreleg of Dog (mm Hg/ml per min)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Dose of cocaine</th>
<th>Vasoactive stimulus *</th>
<th>No. of dogs</th>
<th>Before cocaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg/kg</td>
<td>Norepinephrine 0.5 µg</td>
<td>4</td>
<td>0.68 0.66</td>
</tr>
<tr>
<td></td>
<td>1.0 µg</td>
<td>1.01 0.95</td>
<td>0.02 0.08</td>
</tr>
<tr>
<td></td>
<td>2.0 µg</td>
<td>1.34 1.17</td>
<td>0.04 0.18</td>
</tr>
<tr>
<td></td>
<td>Angiotensin II 0.25 µg</td>
<td>4</td>
<td>0.69 0.71</td>
</tr>
<tr>
<td></td>
<td>0.50 µg</td>
<td>0.68 0.64</td>
<td>0.03 0.01</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>Serotonin 5.0 µg</td>
<td>5</td>
<td>0.42 0.03</td>
</tr>
<tr>
<td></td>
<td>10.0 µg</td>
<td>0.41 0.34</td>
<td>0.64 0.11</td>
</tr>
<tr>
<td>10.0 mg/kg</td>
<td>Norepinephrine infusion (µg/kg/min x 5 min) 0.025 µg</td>
<td>7</td>
<td>0.52 0.42</td>
</tr>
<tr>
<td></td>
<td>0.05 µg</td>
<td>0.79 0.75</td>
<td>0.01 0.05</td>
</tr>
<tr>
<td>5.0 mg/kg</td>
<td>Nerve stimulation 3-6 volts</td>
<td>8</td>
<td>0.40 0.004</td>
</tr>
<tr>
<td></td>
<td>6-12 volts</td>
<td>1.26 0.08</td>
<td>0.91 0.27</td>
</tr>
<tr>
<td></td>
<td>Norepinephrine 1.0 µg</td>
<td>8</td>
<td>0.89 0.83</td>
</tr>
<tr>
<td></td>
<td>2.0 µg</td>
<td>1.14 0.92</td>
<td>0.04 0.18</td>
</tr>
<tr>
<td></td>
<td>Tyramine 25.0 µg</td>
<td>6</td>
<td>0.51 0.45</td>
</tr>
<tr>
<td></td>
<td>50.0 µg</td>
<td>0.78 0.87</td>
<td>0.07 0.02</td>
</tr>
</tbody>
</table>

* Doses of norepinephrine are expressed in terms of the base. The doses of other drugs are in terms of the salt.
† Responses of these animals to norepinephrine are in figure 2.
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0.025 to 0.2 ml and the volumes infused were 0.2 and 0.5 ml/min.

The difference between the maximal increases in pressure in the brachial artery and brachial vein in response to the stimuli was divided by total blood flow to obtain the increase in total foreleg vascular resistance. Changes in arterial, small vessel, and venous resistances were calculated by dividing the difference between maximal increases in pressure in the brachial and metacarpal arteries, the metacarpal artery and vein, and the metacarpal and brachial veins respectively by total blood flow to the foreleg.

In the calculation of segmental resistances using this technique it is assumed that the pressor responses obtained in the small artery and vein in the paw are representative of pressor responses in all small arteries and veins of the same size in the foreleg. This assumption is valid with respect to the drugs used in these experiments. We have measured on several occasions the pressor responses to norepinephrine, angiotensin, serotonin, and tyramine in a small artery and vein in the paw as well as in a small artery and vein in the muscle simultaneously. The responses in small vessels of the paw were similar to those obtained in small vessels of the muscular portion of the perfused foreleg. Therefore, when the pressure gradient from small artery to small vein in the paw is divided by total blood flow the quotient is a valid estimate of the resistance interposed by small vessels of the whole foreleg to total blood flow.

DESIGN AND ANALYSIS OF EXPERIMENTS

The experiments were designed primarily to compare the effect of norepinephrine on vascular segments in the foreleg of dog before and after cocaine. Angiotensin and serotonin were administered as vasoconstrictor agonists to test the specificity of the effect of cocaine on the responses to norepinephrine. The doses of vasoactive drugs and the nerve stimulations were administered in a random order before and after cocaine. Comparison between responses was made by analysis of variance.\(^6\) A quantitative estimate of the super-

<table>
<thead>
<tr>
<th>After cocaine</th>
<th>F — values (\dagger)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>Small vessels</td>
</tr>
<tr>
<td>0.78</td>
<td>0.63</td>
</tr>
<tr>
<td>0.97</td>
<td>0.63</td>
</tr>
<tr>
<td>1.24</td>
<td>0.81</td>
</tr>
<tr>
<td>0.34</td>
<td>0.34</td>
</tr>
<tr>
<td>0.57</td>
<td>0.45</td>
</tr>
<tr>
<td>0.89</td>
<td>0.06</td>
</tr>
<tr>
<td>0.94</td>
<td>0.69</td>
</tr>
<tr>
<td>1.09</td>
<td>0.67</td>
</tr>
</tbody>
</table>

F — values represent the variation ascribed to "sessions" calculated by analysis of variance \(^6\) and indicate the significance of the difference between mean responses obtained before and after cocaine.

\(\dagger\) Indicates \(P < 0.05\).

\(\dagger\) Indicates \(P < 0.01\) and the absence of symbols indicates \(P > 0.05\) or nonsignificance.

* Circulation Research, Vol. XV, September 1964
sensitivity to norepinephrine after 5 mg/kg of cocaine was obtained from dose-response regressions of changes in vascular resistance using the technique of a parallel line bio-assay.7

Results

NOREPINEPHRINE

The smallest dose of cocaine, 0.5 mg/kg, was insufficient to augment the effect of intra-arterial injections of norepinephrine on total vascular resistance in the foreleg but the responsiveness of veins, arteries, and small vessels was altered. The effect of norepinephrine on small vessels decreased and its effect on arteries and veins increased significantly (table 1).

After 5.0 mg/kg of cocaine the increments in total as well as arterial and venous resistances caused by intra-arterial injections of norepinephrine were augmented in each of six dogs but the responses of small vessels declined in four dogs and increased minimally in two (figs. 1 and 2). The maximal augmentation of venous and arterial responses lasted more than 30 minutes (fig. 3).

With intra-arterial infusions of norepinephrine, brachial and small artery pressures increased abruptly and reached a plateau rapidly in another group of nine dogs; the pressor response in the small vein was slower and became maximal after one minute of infusion (fig. 4). As with intra-arterial injections of norepinephrine, cocaine, 5 and 10 mg/kg, sen-
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FIGURE 2

Effects of intra-arterial injections of norepinephrine on total and segmental resistances in the foreleg of six dogs before and after cocaine (5 mg/kg iv). The entries are average values. The statistical significance of the difference between responses obtained before and after cocaine was determined by analysis of variance (table 2). The potency of norepinephrine was calculated with respect to the increases in total, small vessel and venous resistances because the corresponding regressions were linear and parallel and satisfied other requirements for a parallel line bioassay. RP represents the estimated factor by which the sensitivity to norepinephrine was increased and its 95% fiducial limits are based on Fieller's theorem.7

sitized only the arterial and venous segments in each dog to the infusions of norepinephrine (table 1 and fig. 4). The responses of small vessels decreased after cocaine in three of nine dogs, increased slightly in four and did not change in two.

ANGIOTENSIN

Cocaine, 0.5 mg/kg, did not sensitize any of the vascular segments to the constrictor action of angiotensin (table 1). In two other experiments 5 mg/kg of cocaine did not increase the responses to angiotensin at a time when the responses to norepinephrine were augmented (fig. 1).

SEROTONIN

Serotonin dilates small vessels and constricts arteries and veins. After cocaine, 5 mg/kg, the responses to serotonin were not altered significantly in the same dogs which had an augmented response to norepinephrine (table 1, figs. 2 and 5).

NERVE STIMULATION

The responses reported in two of the eight dogs in this group were observed after stimuli of three and six volts. The remaining six dogs did not respond to three volts and observations were made after six and twelve volts. These were not supramaximal stimulations. The longest time interval between periods of stimulation was 15 minutes. The nerves were stimulated immediately before cocaine in five of the eight dogs and immediately after cocaine in four dogs because the stimulations and the injections of norepinephrine and tyramine were administered in random order both before and after cocaine. In the eight dogs one of the two periods of nerve stimulation preceded the injection of cocaine by an average of 4.6 minutes (2 to 8 minutes) and followed it by an average of 6 minutes (4 to 13 minutes). In all dogs a good dose-response regression was observed before cocaine. In three experiments responses to the same stimulus were not reduced over a period of at least 20 minutes without cocaine. In one dog a stimulus of six volts at 20 cycles per second increased perfusion pressure by 32 mm Hg; the increases obtained 13 and 20 minutes later were 28 and 31 mm Hg respectively. In another experiment 12 volts at 20 cycles per second increased perfusion pressure by 125 mm Hg and small vein pressure by 47 mm Hg; the corresponding increases 34 minutes later were 125 and 45 mm Hg. In a third dog
**Analysis of Variance (data from figure 2)***

<table>
<thead>
<tr>
<th>Source of variation</th>
<th>Total</th>
<th>Small vessels</th>
<th>Arteries</th>
<th>Veins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>dF</td>
<td>Mean square</td>
<td>F</td>
<td>Mean square</td>
</tr>
<tr>
<td>Preparations†</td>
<td>1</td>
<td>0.604</td>
<td>15.1 $\dagger$</td>
<td>0.038</td>
</tr>
<tr>
<td>Regression‡</td>
<td>1</td>
<td>1.058</td>
<td>26.4 $\dagger$</td>
<td>0.197</td>
</tr>
<tr>
<td>Parallelism‡</td>
<td>1</td>
<td>0.085</td>
<td>1.6</td>
<td>0.002</td>
</tr>
<tr>
<td>Quadratic</td>
<td>1</td>
<td>0.012</td>
<td>0.3</td>
<td>0.013</td>
</tr>
<tr>
<td>Difference of quadratics</td>
<td>1</td>
<td>0.004</td>
<td>0.1</td>
<td>0.005</td>
</tr>
<tr>
<td>Doses</td>
<td>5</td>
<td>0.348</td>
<td>0.1</td>
<td>0.051</td>
</tr>
<tr>
<td>Dogs</td>
<td>5</td>
<td>0.830</td>
<td>0.1</td>
<td>0.034</td>
</tr>
<tr>
<td>Error</td>
<td>25</td>
<td>0.04</td>
<td>0.037</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Parallel line bio-assay using a symmetrical 6-point design according to methods described by Finney.7
† Variation ascribed to preparations represents the difference between mean responses obtained before and after cocaine.
‡ Significance of regression and nonsignificance of parallelism indicate that the chief requirements for a parallel line bio-assay are satisfied.7
$\dagger$ Indicates $P < 0.01$.
$\ddagger$ Indicates $P < 0.05$.

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**FIGURE 3**

Effects of intra-arterial injections of norepinephrine into the perfused foreleg of a dog before and 20, 30, and 60 minutes after the intravenous administration of cocaine hydrochloride; the exaggerated responses lasted more than 30 minutes.
SENSITIZATION OF BLOOD VESSELS AFTER COCAINE

FIGURE 4

Effects of intra-arterial infusions of norepinephrine into the perfused foreleg of a dog before and after intravenous administration of cocaine. The pressure gradients from brachial artery to small artery and from small vein to brachial vein were greater after cocaine indicating greater constriction of arterial and venous segments. The pressure gradient from small artery to small vein was altered slightly after cocaine indicating the lack of sensitization of small vessels after cocaine.

In all animals cocaine produced small changes in systemic arterial pressure with transient increases in perfusion pressure, small artery, and small vein pressures. Pressures were allowed to return to control levels after cocaine and before the administration of drugs or stimulation of sympathetic nerves (fig. 4). Occasionally with larger doses of cocaine, 5 and 10 mg/kg iv, perfusion pressure and small artery pressure remained slightly elevated.

TYRAMINE

In six of the eight dogs in which the sympathetic nerves were stimulated, cocaine (5 mg/kg) suppressed the vasoconstrictor action of intra-arterial tyramine on small vessels. The effect of tyramine on veins and arteries was negligible both before and after cocaine (table I, fig. 6).

EFFECT OF THE INTRAVENOUS INFUSIONS OF COCAINE

In six of the eight dogs in which the sympathetic nerves were stimulated, cocaine (5 mg/kg) suppressed the vasoconstrictor action of intra-arterial tyramine on small vessels. The effect of tyramine on veins and arteries was negligible both before and after cocaine (table I, fig. 6).

Increases in perfusion pressure in response to stimuli of three and six volts at 20 cycles per second were 45 and 100 mm Hg; corresponding responses 24 and 27 minutes later were 42 and 105 mm Hg respectively. These observations suggest that the responses to nerve stimulation did not tend to diminish spontaneously with time in these experiments.

The effect of nerve stimulation on the vascular segments differed from that of intra-arterial norepinephrine. Nerve stimulation constricted primarily venous and arterial segments while norepinephrine constricted mainly the small vessel segment (table 1). Cocaine slightly reduced the responses of all segments to nerve stimulation (table 1, fig. 6). In this, as in the other groups of dogs, the effects of norepinephrine on total, venous, and arterial resistances were augmented after cocaine.

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FIGURE 5
Effects of intra-arterial injections of serotonin into the perfused foreleg of a dog before and after intravenous administration of cocaine hydrochloride. The pressor effects of cocaine were transient (middle frames). Serotonin dilates small vessels causing a fall in small artery pressure and constricts venous and arterial segments causing the rises in small vein and brachial artery pressures. Cocaine did not alter the effects of serotonin significantly.

FIGURE 6
Effects of sympathetic nerve stimulation, intra-arterial injections of norepinephrine and tyramine before and after intravenous administration of cocaine. The vasoconstrictor effect of norepinephrine was augmented, that of nerve stimulation was reduced, and that of tyramine was suppressed.
Sensitization of Blood Vessels After Cocaine

Discussion

If we had measured only perfusion pressure the results would have suggested that 0.5 mg/kg of cocaine did not alter the vasoconstrictor action of norepinephrine since the increase in total resistance across the foreleg was not enhanced. Actually, there was sensitization of venous and arterial segments which was accompanied by a decreased response in the small vessel segment. The net effect of these opposite changes in sensitivity was an increase in total resistance similar to that observed before cocaine. We were unable to demonstrate any significant increase in sensitivity of the small vessels to norepinephrine by increasing the dose of cocaine to 5 or 10 mg/kg.

Angiotensin and serotonin were selected to test the specificity of the supersensitivity to norepinephrine because angiotensin constricts small vessels predominantly and serotonin constricts arterial and venous segments. Their effects were not enhanced by cocaine. In most instances the peak pressor response occurred in all vessels simultaneously. In some experiments the peak response in small veins occurred a few seconds later than the peak response in the small arteries. This temporal effect had no significant influence on our results because in several experiments, especially after cocaine, the peak response in the small artery was sustained even after the venous pressure began to decline (fig. 3). The experiments in which norepinephrine was infused were done to ascertain that the slightly asynchronous peak responses following intra-arterial injections did not affect our conclusions. The results obtained with intra-arterial infusions during which the maximal responses were maintained at all four sites for at least a minute or more are in agreement with those obtained with intra-arterial injections (fig. 4).

Perhaps the most important conclusion which may be drawn from these experiments is that the phenomenon of vascular supersensitivity to norepinephrine after cocaine is not uniform but may be restricted to certain vascular segments. Previous experiments reported from this laboratory indicate that increased vascular sensitivity after reserpine also is not uniform; the veins of the foreleg were not affected when other vascular segments were sensitized.

Three implications may be considered in connection with the responses seen after cocaine. The first concerns a qualitative change in the cardiovascular effect of norepinephrine. In intact animals norepinephrine does not change cardiac output significantly. The greater vasoconstrictor action observed after cocaine could increase both cardiac filling pressure and cardiac output. The second implication deals with the mechanism of increased sensitivity. Cocaine delays inactivation of injected norepinephrine and increases the concentration of the catecholamine in plasma. Trendelenburg suggested that the larger amount of circulating norepinephrine after cocaine produces the augmented response. If circulating norepinephrine were solely responsible for the greater increase in vascular resistance one would expect an increase in responses of all vascular segments. Since the sensitization was selective a local effect of cocaine on the mobilization of norepinephrine in the walls of blood vessels may differ in one vascular segment as compared to another. The third implication relates to the decreased response to tyramine which accompanies the supersensitivity to norepinephrine. Tyramine mainly constricts small vessels. After cocaine the action of tyramine is suppressed at a time when the action of norepinephrine is only slightly increased. In contrast, after reserpine the response to tyramine is only moderately reduced and the sensitivity to norepinephrine is several times greater than after cocaine. If equally small amounts of norepinephrine were released by tyramine after cocaine and after reserpine one might expect the difference in responses since the small vessels upon which tyramine acts primarily appear to be sensitized after reserpine but not after cocaine.

The information available in the literature on the effect of cocaine upon nerve stimulation deals with responses of nictitating membranes. Fleckenstein and Bass reported that
cocaine failed to increase the response of the nictitating membrane to submaximal nerve stimulation although it potentiated the response to injected norepinephrine. In contrast Trendelenburg reported more recently that cocaine increased the response of the nictitating membrane of the spinal cat to weak submaximal preganglionic stimulation as much as to injections of norepinephrine; the response to supramaximal nerve stimulation was not affected by cocaine. The results we obtained with stimulation of the nerve supply to blood vessels did not permit us to conclude that cocaine augmented the responses to either weak or strong stimuli. This difference between responses of nictitating membranes and blood vessels is not unique. Previous observations indicated that sensitization of the nictitating membrane by cocaine is much more pronounced than that of the cardiovascular system. Fleckenstein and Bass suggested that cocaine might reduce the liberation of norepinephrine during nerve stimulation so that the response of blood vessels might decline in spite of the increased sensitivity to injected norepinephrine. Recent observations by Kirpekar and Cervoni indicate, however, that the output of catecholamine with nerve stimulation of the spleen and adrenal medulla is not decreased after cocaine.

The mechanisms involved in the action of cocaine are unknown. Any attempt to explain the reason for the supersensitivity of the arterial and venous segments but not of the small vessels segment would be speculative. There is increasing evidence for the view that cocaine causes supersensitivity by preventing uptake of norepinephrine in tissue "stores" so that more hormone becomes available to the receptor sites. Furchgott et al. suggested that the spatial arrangement of receptors and nerve terminals or "stores" may be of importance in determining the effect of cocaine. If the receptor is very close to the nerve ending then the uptake by the "store" must be very important for the regulation of the concentration of norepinephrine at the receptor and consequently the sensitization caused by cocaine would be pronounced. If the receptor is at a distance from the "store" cocaine would be less effective in potentiating the effect of norepinephrine. The large constriction of arterial and venous segments, but not of small vessels following the stimulation of the sympathetic nerve, suggests a closer proximity between "stores" and receptors in arteries and veins than in small vessels. If such a relationship actually existed the selective sensitization of arteries and veins caused by cocaine would be in agreement with the hypothesis proposed by Furchgott et al.

Summary

The effects of cocaine on the responses of arteries, veins, and small vessels to norepinephrine were studied. Intra-arterial norepinephrine was injected or infused into perfused forelegs of dogs. Angiotensin and serotonin were used as agonists. The effects of postganglionic sympathetic stimulation and of intra-arterial tyramine were tested also.

Cocaine in doses of 0.5, 5.0, and 10 mg/kg iv sensitized the arterial and venous segments to norepinephrine; the responses of small vessels were not augmented significantly. The effects of angiotensin and serotonin were not increased. The vasoconstrictor effect of weak and strong submaximal postganglionic sympathetic nerve stimulations was reduced and that of intra-arterial tyramine was suppressed after cocaine.

The results allow us to conclude that vascular supersensitivity to norepinephrine after cocaine is not a uniform phenomenon but it is restricted to certain vascular segments. The reason for the sensitization of arteries and veins but not small vessels is unknown. The observations are discussed in light of the recent hypothesis proposed by Furchgott et al. on the mechanism of action of cocaine.

References

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