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### Research Article

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# Mechanisms of Reflex Vasodilation: Assessment of the Role of Neural Reuptake of Norepinephrine and Release of Histamine

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**ABSTRACT** The mechanisms of reflex vasodilation were studied in an innervated canine hind-limb preparation which was perfused at a constant rate. Reflex vasodilation was produced by suddenly increasing the pressure in the trunk by the intravenous injection of norepinephrine, with consequent stimulation of the baroreceptors. When the basal vasoconstrictor tone exerted by the sympathetic nervous system on the systemic arterial bed was minimized, either by pretreatment with the alpha adrenergic blocking agent phenoxybenzamine or with reserpine, which depletes endogenous catecholamine stores, reflex vasodilation was virtually abolished. Administration of cocaine, a drug which blocks reuptake of norepinephrine by the nerve terminals, significantly reduced reflex vasodilation, the response after cocaine averaging 47% of the vasodilator response in the control period. Cocaine also potentiated the vasoconstriction caused by intra-arterially administered norepinephrine but attenuated the vasoconstriction induced by tyramine. The antihistamine, tripeleminamine, had effects similar to those of cocaine. It is suggested, therefore, that reflex vasodilation results from a sudden decrease in the level of norepinephrine at the neuroeffector junction, which is a consequence of the cessation of norepinephrine secretion, together with continued and possibly augmented uptake. When the uptake mechanism is impaired, either by the administration of cocaine

or tripeleminamine, the magnitude of reflex vasodilation is diminished. It does not appear necessary to postulate active secretion of a vasodilator substance to account for reflex vasodilation.

## INTRODUCTION

It is well established that reflex dilation of the arterial bed occurs when the baroreceptors located within the aortic arch and carotid sinus areas are activated by an elevation in intravascular pressure. The mechanism causing this vasodilation, however, has been a source of controversy, and two major schools of thought have emerged. One group of investigators feels that reflex vasodilation can be completely accounted for by postulating a shutting off of norepinephrine secretion at the neuroeffector junction (1, 2). This mechanism of chemical mediation has been termed the *passive* form of vasodilation. The other group of investigators, while admitting the existence of passive vasodilation, suggests that a large component of reflex vasodilation results from neural secretion of a substance with vasodilator properties (3-5). This mechanism has been termed the *active* form of vasodilation. Furthermore, because certain antihistamines considerably reduce the magnitude of reflex vasodilation, it has been suggested that histamine is probably the mediator of the active component of vasodilation (6, 7).

In recent years studies from several laboratories have helped to clarify the fate of norepinephrine released at the neuroeffector junction. It is now

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evident that the concentration and, therefore, the activity of norepinephrine at the neuroeffector junction is the net result of the balance between neural secretion, which tends to increase its concentration, and enzymatic degradation, diffusion into the blood stream, and reuptake by the nerve terminals, which tend to decrease its concentration (8-10). These studies indicate that reuptake by the nerve endings is the principal physiologic means by which the action of norepinephrine at the neuroeffector junction is terminated (11). However, the relevance of these observations to reflexly induced vasodilation has not been previously investigated.

The aim of the present investigation was to define the mechanisms responsible for the production of reflex vasodilation by first, reinvestigating the role of possible neurogenic histamine secretions, second, by evaluating critically the role of the neural reuptake process in the production of reflex vasodilation, and, third, by studying the mechanism of action of antihistamines in the suppression of reflex dilation.

## METHODS

28 dogs, ranging in weight from 15.9 to 25.0 kg, were studied in which the normally innervated hindlimb was perfused at a constant flow rate. Changes in perfusion pressure, therefore, reflected changes in limb vascular resistance. The animals were anesthetized with a combination of chloralose, 48-96 mg/kg i.v., and urethane 480-960 mg/kg i.v. Except for four of the six reserpine-treated dogs, they were also premedicated with morphine sulfate, 3 mg/kg s.c.

Reflex vasodilation in the innervated, perfused limb was produced by raising systemic arterial pressure by the intravenous administration of norepinephrine. To insure that the blood flow was directed predominantly to the vascular bed of skeletal muscle, the paw was amputated and the skin of the hindlimb removed. The limb was then wrapped in towels which had been soaked in warm saline. A thermistor probe was placed at the surface of the limb, and a second thermistor was inserted into the external jugular vein; in all experiments the temperature in the trunk and hindlimb were then maintained in the physiologic range. Both vagus nerves were sectioned in the neck to nullify the effects of stimulating the aortic arch baroreceptors. The animals were allowed to breathe spontaneously; oxygen was administered at a rate of 2 liters/min through a catheter inserted into an endotracheal tube.

The lower abdominal aorta, exposed through an abdominal incision, was cannulated and blood was permitted to flow from the aorta into a 1500 cc capacity reservoir which had initially been primed with 1000 ml of blood

obtained from donor dogs and then thoroughly mixed with that of the experimental animal. From the reservoir, blood was pumped at a constant flow rate by a Sigmamotor pump, via a heat exchanger, into the distal end of the external iliac artery through a large metal cannula. Blood flow from the pump was kept constant throughout each study, and the range in different experiments was from 68 to 116 ml/min. To eliminate possible collateral channels to the limb, the aorta was ligated above the trifurcation, as were the inferior mesenteric, ovarian or spermatic, and deep circumflex iliac arteries, the middle sacral trunk, and all accessible lumbar arteries (2). Perfusion pressure in the limb was recorded from a catheter inserted into the deep femoral artery with the tip distal to the perfusing cannula; trunk pressure was recorded from the brachial artery. Intra-arterial injections were made through a two-way stopcock proximal to the pump, and the amount injected was usually 0.2 ml. Injections of similar amounts of saline were made frequently to serve as controls.

To clarify the possible role of neurogenic histamine release in the production of reflex vasodilation, two sets of experiments were performed in which the basal adrenergic tone exerted by the sympathetic nervous system on the arterial bed was minimized, with the hope that the vasodilator effect of any released histamine could thereby be identified. In the first set, blockade of the alpha adrenergic receptors was produced in seven dogs by pretreatment with phenoxybenzamine in divided doses, 5 mg/kg i.v. 3 days before, 1 day before, and on the morning of the study. Administered in this fashion, this total dose of 15 mg/kg of phenoxybenzamine resulted in maximal blockade of the alpha adrenergic receptors without making the vascular bed unreactive (12). In the second set of experiments, basal adrenergic tone was eliminated in six animals by depletion of endogenous catecholamine stores. These dogs received a total dose of 0.4-0.6 mg/kg of reserpine administered intravenously in two equally divided doses on each of the 2 days preceding the experimental procedure.

To investigate the physiologic importance of neural reuptake of norepinephrine on reflex vasodilation, six dogs were studied before and after the reuptake process had been impaired by the acute administration of cocaine hydrochloride, 2.5-10 mg/kg of total body weight, injected into the cannula perfusing the limb (13-15). In addition, dose-response curves to norepinephrine and to tyramine administered directly into the perfused limb were performed. The doses of norepinephrine administered as the free base ranged from 0.01 to 0.50  $\mu$ g/kg of total body weight, and the doses of tyramine ranged from 1 to 40  $\mu$ g/kg.

In order to elucidate the mechanism of action of antihistamines on reflex vasodilation, studies similar to those carried out before and after treatment with cocaine were performed in another group of nine dogs before and after the administration of tripeleminamine hydrochloride. Five of these animals received 3 mg/kg directly into the limb, one received 1 mg/kg, two were given 0.5 mg/kg, and one was treated with 0.25 mg/kg.

## RESULTS

Typical responses obtained in the control period from two different dogs are illustrated in Fig. 1 and demonstrate the magnitude of reflex vasodilation obtained in the perfused hindlimb as a result of raising trunk pressure with the intravenous injection of norepinephrine. In 11 animals during the control period, when trunk pressure was raised by an average value of  $27 \pm 3.1\%$  (SEM) with injected norepinephrine, a reflex fall averaging  $46 \pm 2.7\%$  was produced in the perfusion pressure, reflecting substantial decreases in hindlimb vascular resistance (Fig. 2). However, when the basal vasoconstrictor tone exerted by the sympathetic nervous system on the arterial bed had been blocked by chronic pretreatment with the alpha adrenergic blocking agent, phenoxybenzamine, despite an average rise in trunk pressure of  $36 \pm 5.7\%$ , reflex vasodilation was completely blocked in five dogs, was attenuated in one dog, and was at the lower end of the normal range in

the seventh dog (Fig. 2). It is of interest that in four animals subjected to alpha receptor blockade, administration of histamine,  $0.1-1.0 \mu\text{g}/\text{kg}$ , directly into the perfused limb produced an average fall in perfusion pressure of  $31 \pm 8.5 \text{ mm Hg}$ . In the group of six dogs in which basal adrenergic tone had been reduced by pretreatment with reserpine with consequent depletion of endogenous catecholamines, reflex vasodilation was essentially abolished in all instances, despite an average rise of  $49 \pm 13.7\%$  in the trunk pressure (Fig. 2). Although reflex vasodilation was blocked by previous reserpine treatment, the hindlimb vascular bed was still reactive, as shown by marked vasoconstriction produced by norepinephrine injected directly into the limb and by vasodilation caused by isoproterenol. Moreover, acetylcholine,  $0.05-0.5 \mu\text{g}/\text{kg}$ , administered directly into the perfused limb produced a fall in perfusion pressure in five dogs treated with phenoxybenzamine of  $46 \pm 13 \text{ mm Hg}$  and a fall in perfusion pressure in four dogs treated with reserpine of  $48 \pm 22 \text{ mm Hg}$  which

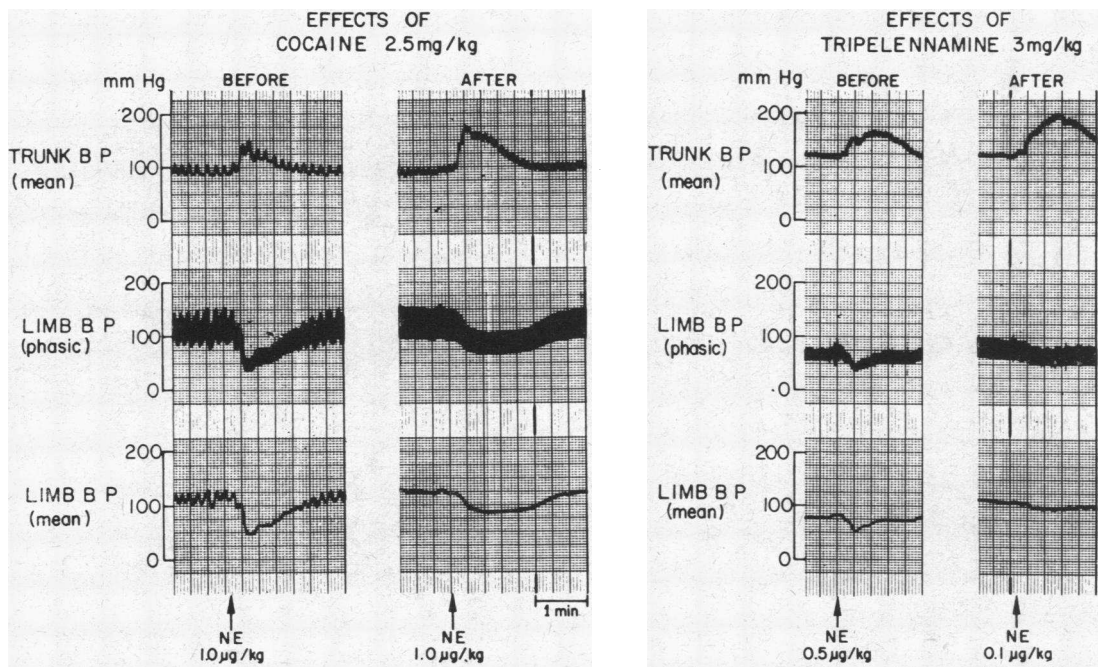


FIGURE 1 Left: Effects of cocaine on reflex vasodilation in the perfused hindlimb produced by raising trunk blood pressure (BP) with intravenous administration of norepinephrine (NE). After treatment with cocaine, the extent of reflex vasodilation was considerably reduced, despite the greater pressor effect in the trunk. Right: Effects of triplennamine on reflex vasodilation. This drug resembled cocaine in its ability to obtund reflex vasodilation, while potentiating the pressor effect of injected norepinephrine in the trunk. These actions can be explained by blockade of neural uptake of norepinephrine by triplennamine and by cocaine.

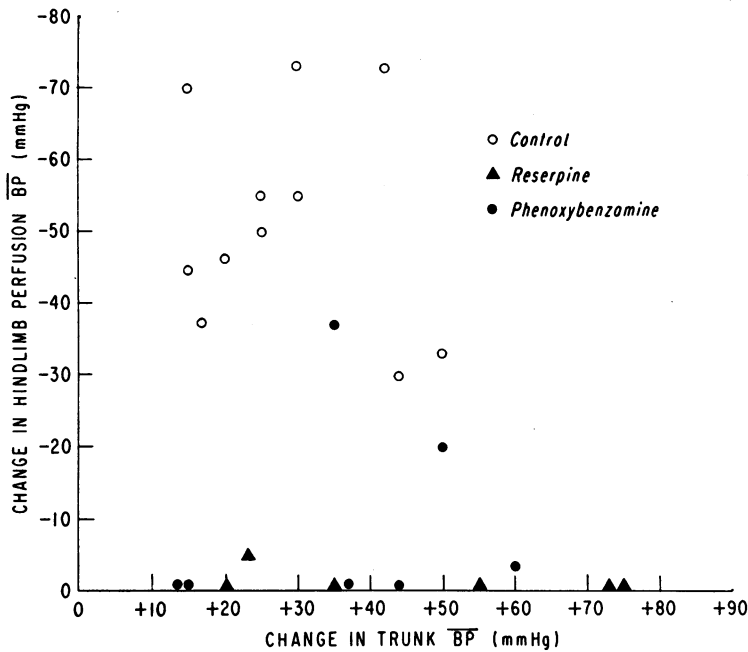


FIGURE 2 Reflex decreases of mean perfusion pressure in the hindlimb produced by suddenly increasing trunk pressure with the intravenous administration of norepinephrine. Pretreatment with reserpine (closed triangles) or with phenoxybenzamine (closed circles) resulted in marked diminution of the reflex vasodilator response compared to control animals (open circles).

also demonstrates that the vascular bed retained its capacity for vasodilation.

When the reuptake of norepinephrine by the nerve terminals was impaired by the acute administration of cocaine, reflex dilation, though still present, was markedly attenuated, the response after cocaine averaging  $47 \pm 1.4\%$  of the vasodilator response observed in the control period (Fig. 3). This diminution in the extent of reflex

vasodilation occurred despite the fact that the rise in trunk pressure produced by intravenous norepinephrine after blockade with cocaine was equal to or greater than the rise before blockade (Fig. 1, left, and Fig. 3). Furthermore, the importance of the reuptake mechanism in the handling of norepinephrine at the arterial neuroeffector junction is demonstrated by the opposite effects cocaine had on the dose-response curves to intra-arterially

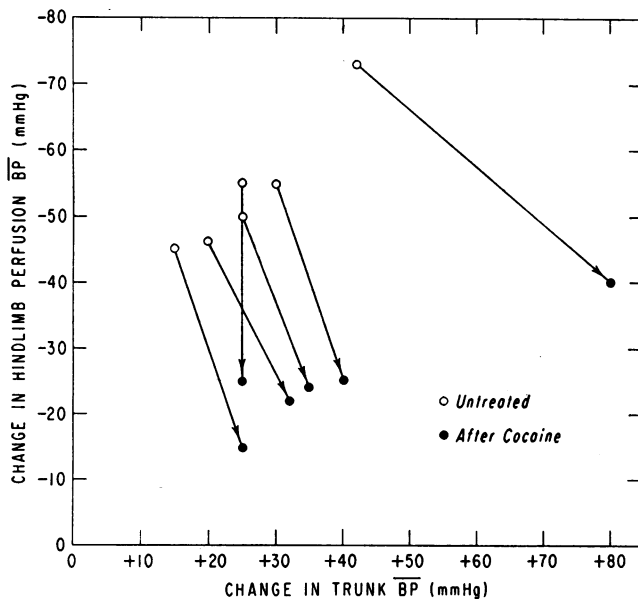


FIGURE 3 Effects of treatment with cocaine on the extent of reflex vasodilation. The magnitude of reflex vasodilation is plotted as a function of the induced rise in trunk pressure during the control period (open circles) and after treatment with cocaine (closed circles). Administration of cocaine reduced the amount of reflex vasodilation in every animal.

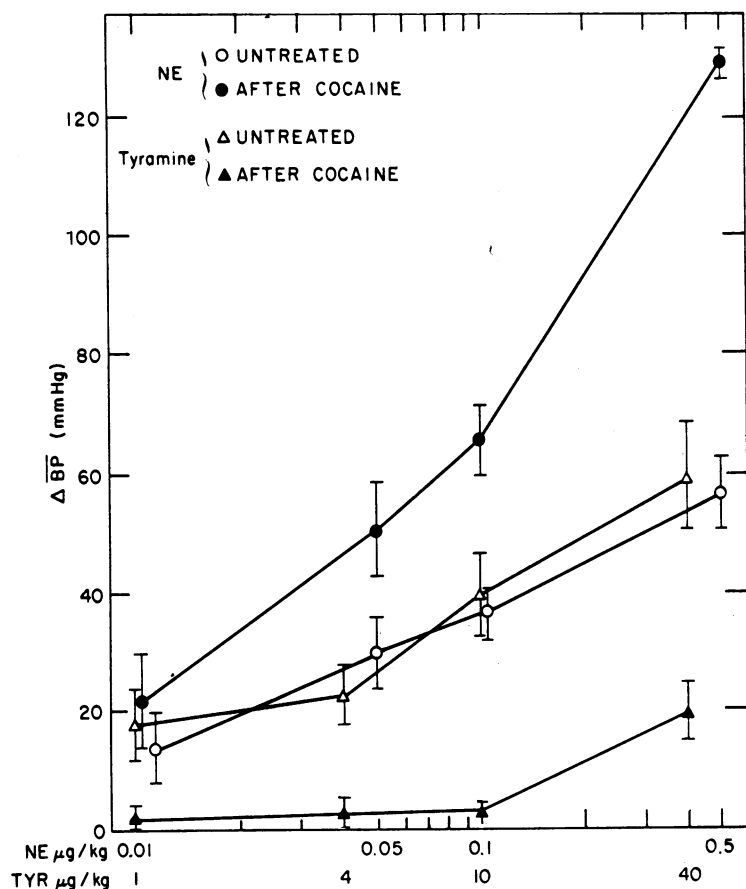


FIGURE 4 Effects of treatment with cocaine on the dose-response curves to norepinephrine (NE) and tyramine (TYR) injected into the perfused hindlimb circulation. The control curve for norepinephrine (open circles) was similar to the control curve for tyramine (open triangles). However, the response to norepinephrine was potentiated by cocaine (closed circles), while the response to tyramine was diminished (closed triangles). Drug dosages are plotted on a logarithmic scale. Vertical bars represent standard error of the mean.

administered norepinephrine and tyramine. During the control period in six studies, doses of these two drugs were administered which produced equipressor responses (Fig. 4). However, after the administration of cocaine marked differences were produced: the vasoconstrictor response to norepinephrine was potentiated whereas the response to tyramine was markedly attenuated (Fig. 4).

The animals in which the effects of treatment with an antihistamine on reflex vasodilation were studied may be divided into two groups. In five dogs a relatively large dose of tripeleennamine, 3 mg/kg, was used because this has been the dose generally employed by previous investigators (7). In four other dogs a smaller dose, ranging from 0.25 to 1 mg/kg, was used. In each of the five dogs that received the larger dose of tripeleennamine, the extent of reflex vasodilation after treatment with the antihistamine was significantly reduced, averaging  $40 \pm 10.5\%$  of the control vasodilator response (Fig. 5). This decrease in the

dilator response occurred despite norepinephrine-induced increases in trunk pressure after tripeleennamine which were equal to or greater than those produced before such treatment (Fig. 5). In addition, just as with treatment with cocaine, administration of tripeleennamine markedly depressed the dose-response curve to tyramine at all the dose levels investigated (Fig. 6). However, the dose-response curve to norepinephrine was not consistently potentiated. Because it was suspected that the lack of potentiation was related to the large dose of tripeleennamine which had been given, dose-response curves to norepinephrine were performed in four dogs before and after smaller doses of tripeleennamine. In these four studies significant potentiation of norepinephrine-induced constriction was present in each instance at the highest dose of norepinephrine used ( $P < 0.05$ ) (Fig. 7, left), although potentiation was not present at the lower doses. As with the larger doses of tripeleennamine, the response to tyramine was markedly

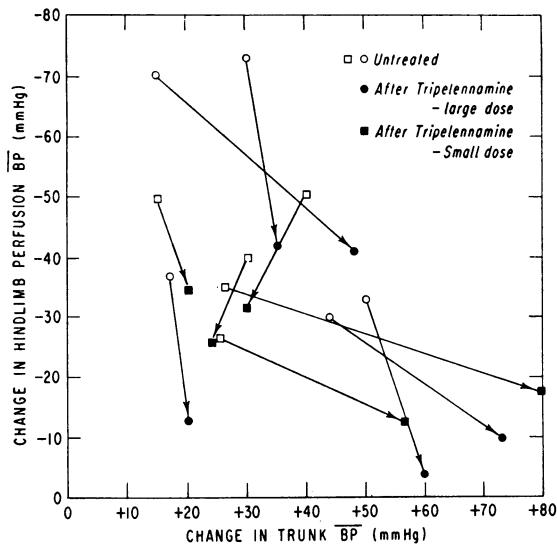


FIGURE 5 Effect of treatment with large and small doses of tripelennamine on the magnitude of reflex vasodilation in the perfused hindlimb. Open symbols represent the extent of reflex vasodilation plotted as a function of the induced rise in trunk pressure during the control period. Closed circles depict the effects of treatment with large doses of tripelennamine and closed squares the effects of small doses of tripelennamine on the amount of reflex vasodilation. After treatment, reflex vasodilation was decreased in each instance.

attenuated in the three dogs studied after small doses of tripelennamine (Fig. 7, right). As shown in Fig. 5, the extent of reflex vasodilation after the small doses of tripelennamine was also diminished, averaging  $69 \pm 9.6\%$  of the control vaso-dilator response.

## DISCUSSION

Although it is generally acknowledged that nor-epinephrine is the chemical mediator of neurally induced arterial vasoconstriction, the intimate chemical mechanisms involved in reflex arterial vasodilation have not been completely elucidated. The role of possible neurogenic release of histamine was studied in animals in which the basal vasoconstrictor tone exerted by the sympathetic nervous system on the arterial bed of skeletal muscle was minimized, with the hope that the vasodilator effect of any released histamine could thereby be uncovered. Two types of experiments were performed to eliminate the effects of basal adrenergic tone: in the first set, the alpha adrenergic receptors were blocked by pretreatment with phenoxybenzamine; in the second set, the endogenous stores of norepinephrine were de-

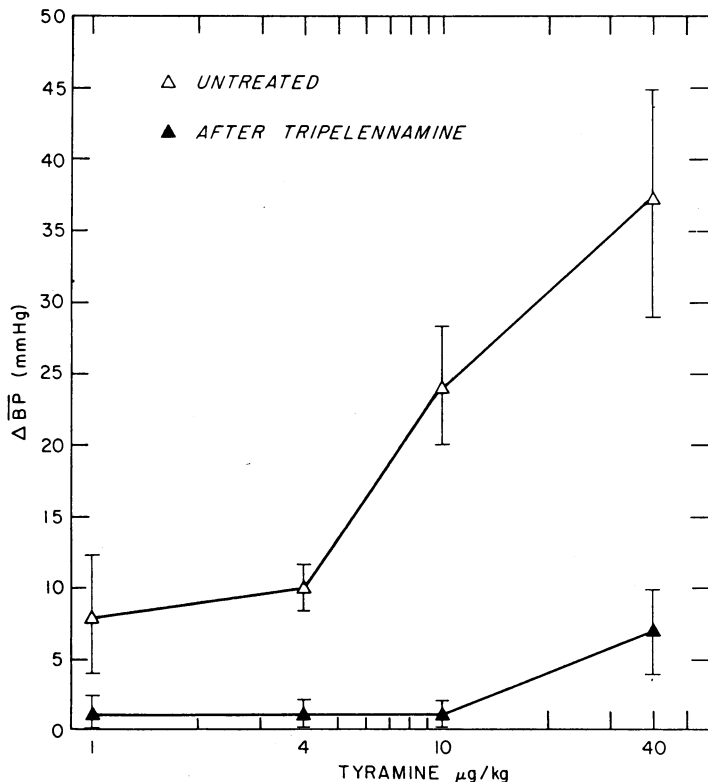


FIGURE 6 Effect of treatment with tripelennamine, 3 mg/kg, on the dose-response curve to tyramine injected into the circulation of the perfused hindlimb. After treatment (closed triangles) the dose-response curve was markedly depressed compared to control values (open triangles). Drug dosages are plotted on a logarithmic scale. Vertical bars represent standard error of the mean.

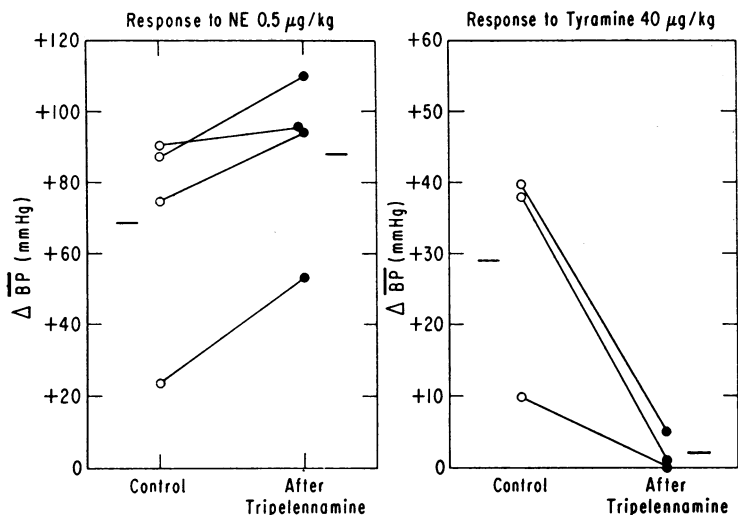


FIGURE 7 Effects of treatment with low doses of tripeleonnamine on the responses to norepinephrine and tyramine injected into the circulation of the perfused hindlimb. The left panel illustrates the potentiation of the constrictor effect of norepinephrine (*NE*) after administration of tripeleonnamine, while the right panel depicts the marked diminution of constriction produced by tyramine after tripeleonnamine.

pleted by pretreatment with reserpine. In the seven dogs subjected to alpha adrenergic blockade, reflex vasodilation was completely blocked in five, was attenuated in one, and was at the lower end of the normal range in the remaining one (Fig. 2). It is known, however, that drugs of the phenoxybenzamine group have modest antihistaminic properties (16), and the lack of vasodilation could possibly be attributed to this effect, rather than to the lack of basal adrenergic tone which was produced as a consequence of the alpha blockade. However, in four animals histamine was injected intra-arterially, and marked vasodilation was produced despite alpha blockade, suggesting that if histamine were important in neurogenic vasodilation its action should have been observed even in the presence of phenoxybenzamine. These results are consonant with those of Folkow and Uvnäs who blocked the alpha receptors with dibenamine (1).

In the six dogs that were treated with reserpine to deplete the endogenous catecholamine stores, reflex vasodilation was essentially abolished. Reserpine, itself, does not have antihistaminic properties nor does it deplete the body of histamine stores, except in the stomach, where it appears to stimulate the parasympathetic nervous system (17). Therefore, it is felt that if active neurogenic histamine release is of importance in reflex vasodilation, such vasodilation should have been manifest in the reserpine-treated animals, since in these dogs the so-called histaminergic nerves would have been free to exert their influence in

relatively pure form. On the other hand, if vasodilation were the result only of decreasing levels of norepinephrine at the neuroeffector junction, the observed abolition of vasodilation after reserpine treatment would be expected. Although details are not given, Beck and Brody state that they have also noted that treatment with reserpine abolishes reflex vasodilation, but they do not reconcile this finding with their conclusion that reflex vasodilation results largely from the active secretion of a vasodilator substance (6).

Similarly, the sympathetic cholinergic system does not appear to participate in reflex vasodilation, since the vascular beds that had been treated with phenoxybenzamine and with reserpine did not display reflex vasodilation, although they retained their sensitivity to intra-arterially injected acetylcholine. This conclusion has also been reached by other investigators (18). Inasmuch as significant reflex vasodilation was virtually absent in these two groups of dogs with low basal adrenergic tone, it is suggested that decreasing levels of norepinephrine at the neuroeffector junction, rather than secretion of histamine or acetylcholine, is the cause of reflex vasodilation.

However, the decrease in norepinephrine levels is a dynamic process which probably involves not only a cessation of secretion but also a continuation or augmentation of reuptake by the nerve terminals. To investigate this problem, a group of animals was studied in which the reuptake process was impaired by the administration of cocaine (13-15). In these dogs, reflex vasodilation was still



present after treatment with cocaine, but the extent of this vasodilation was markedly attenuated when compared to the control vasodilator response. These data are consistent with the hypothesis that when vasodilator reflexes are invoked the decrease in norepinephrine levels at the neuroeffector junction and, therefore, the amount of vasodilation, are dependent both on the reuptake mechanism and on the cessation of active secretion. That is, when one of the means for reducing the norepinephrine concentration at its site of action is inhibited, the amount of vasodilation which can occur is consequently diminished. Furthermore, the importance of the norepinephrine reuptake mechanism at the arterial neuroeffector junction is demonstrated by the contrasting effects which cocaine has on vasoconstriction induced by norepinephrine and by tyramine. Thus, while the vasoconstrictor action of norepinephrine is potentiated, that of tyramine is diminished. This apparent paradox noted by Tainter and Chang in 1927 (19) is explicable by blockade of a neural uptake mechanism which prolongs the time norepinephrine remains in contact with the effector sites, thereby increasing its effective concentration with consequent potentiation. On the other hand, by preventing uptake of tyramine, a drug which acts by displacing norepinephrine from the nerve endings, cocaine reduces the extent of tyramine-induced constriction (20, 21).

It has been reported that antihistamines significantly block reflex vasodilation, and these observations have been cited as evidence for the existence and importance of neurogenic histamine secretion (5-7). Our experiments also show that the antihistamine, tripeleennamine, can indeed diminish the magnitude of reflex vasodilation. However, it is of interest that in the original reports describing the antihistaminic properties of tripeleennamine, it was noted that it had certain cocaine-like effects, such as potentiation of the action of epinephrine on arterial pressure and on the nictitating membrane (22-24). More recently, Isaac and Goth utilizing radioactive norepinephrine demonstrated that both tripeleennamine and chlorpheniramine potentiated the heart rate response of isolated atria to norepinephrine and depressed the uptake of norepinephrine by ventricular myocardium (25). That is, these antihistamines behaved like cocaine. Our studies also demonstrate that tripeleennamine

mimics cocaine in several ways. Not only did it diminish the extent of reflex vasodilation as did cocaine, but it also depressed the dose-response curve of intra-arterially administered tyramine. Thus, it seems likely that both cocaine and tripeleennamine depress the neural uptake of tyramine, thereby attenuating its vasoconstrictor action. In addition, in low doses tripeleennamine also potentiated the vasoconstriction caused by intra-arterial norepinephrine administration. It is probable, therefore, that the inhibiting effects on reflex vasodilation which have been noted after treatment with certain antihistamines result not from their ability to antagonize the effects of histamine, but rather from their cocaine-like action which produces blockade of neural uptake of norepinephrine.

In addition to the inhibiting action of antihistamines, arguments supporting an active vasodilator mechanism have revolved around the observation that the magnitude of dilation produced reflexly is greater than the sustained dilation which occurs when the sympathetic innervation is interrupted surgically (4, 26). It has been assumed that the sustained vasodilation which persists after sympathectomy represents the contribution resulting from withdrawal of basal sympathetic tone, whereas the difference between this level of vasodilation and the still greater vasodilation which can be produced reflexly or as a result of acute denervation represents the contribution of active secretion of a vasodilator substance. The proponents of the active secretion theory of vasodilation have not discussed possible alternative explanations for this difference in extent of vasodilation produced reflexly and by sympathectomy. One of the well-described properties of a denervated vascular bed is autoregulation (27). That is, when pressure is suddenly lowered, in a constant flow system, it would be expected that vascular resistance would rise over the course of several minutes to some intermediate level as a result of the process of autoregulation. This interpretation would be consistent with either the myogenic (28) or metabolic theory (29) of autoregulation. Thus, a well described mechanism which is known to affect arterial resistance could explain many of the observations which have been made, without invoking the theory of active secretion of a vasodilator substance.

Recently, Brody has reported that reflex vasodilation produced in an isolated perfused muscle preparation releases increased amounts of radioactive histamine and *N*-methylhistamine into the venous effluent (30). However, the priming dose of radioactive histamine was large and undoubtedly entered many areas of tissue water in a non-specific fashion. The reflex dilation which was then produced could very well have washed out increased amounts of radioactivity by a redistribution of blood flow. An attempt was made to obviate this possibility by producing a comparable amount of vasodilation by intra-arterial injection of nitroglycerine. However, the redistribution of blood flow caused by intra-arterial administration of nitroglycerine may be different from the redistribution induced by a reflex vasodilator mechanism. It has been shown, for instance, that in the coronary arterial bed nitroglycerine acts on the large arteries but not on the smaller arterioles, which are generally considered to be the prime site of neural activation (31). The argument that the increased radioactivity coming from the limb may be nonspecific in nature is strengthened by the fact that a large amount of the total radioactivity appeared as *N*-methylhistamine. The soluble methylating enzyme is widely distributed in the tissue water (32), and, moreover, it has recently been shown that the physiologic metabolites of histamine are acid products and not methylhistamine (33). Thus, the finding of a significant increase in methylhistamine favors the nonspecific releasing action of redistribution of blood flow and blood volume rather than release from "histaminergic" nerves.

From the results presented herein, it is concluded that reflex vasodilation can be accounted for solely by a sudden decrease in the concentration of norepinephrine at the neuroeffector junction, without postulating secretion of a vasodilator substance. It is suggested that the decrease in norepinephrine level results from the cessation of secretion, coupled with the continuation and possible augmentation of neural reuptake. When the reuptake mechanism is impaired, reflex vasodilation is significantly diminished. Finally, it appears that the inhibiting effect certain antihistamines have on reflex vasodilation can be attributed to their cocaine-like ability to interfere with the

neural reuptake mechanism, rather than to their ability to antagonize the effects of histamine itself.

#### ACKNOWLEDGMENT

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