Nature of the Vasodilator and Vasoconstrictor Receptors in Skeletal Muscle of the Dog

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Femoral blood flow and arterial pressure responses to stimulation of the lumbar sympathetic chain at L3, L4 and L5 were compared with responses to intra-arterial injections of l-epinephrine and l-norepinephrine before and after progressively increasing levels of adrenergic blockade, and after atropine. The vasoconstrictor responses to nerve stimulation resembled most closely those caused by l-norepinephrine injections at all levels of blockade. Atropine blocked the dilator responses to sympathetic nerve stimulation and reduced reversal responses to l-norepinephrine injections but had no effect on the dilator responses to l-epinephrine. It is concluded that, in skeletal muscle, there are three types of vasoreceptors under autonomic control. Two of these, one constrictor and one dilator, are innervated; the third, a dilator receptor, is only under hormonal control.

Four main mechanisms have been postulated to explain excitation or inhibition of vascular smooth muscle by adrenergic nerve impulses:

1. L-epinephrine is the chemical mediator of the adrenergic nerve impulses everywhere, producing both excitatory and inhibitory effects.1, 2

2. L-epinephrine, or a substance like it (Mediator M), is liberated by sympathetic nerves and changed at the site of action to produce the active substances Sympathin E and Sympathin I, which are different from epinephrine and norepinephrine.3

3. L-norepinephrine (Sympathin N) is the chemical transmitter in some areas and l-epinephrine (Sympathin A) in others. Both inhibitory and excitatory effects are produced by the two ergones.4

4. L-epinephrine is liberated by sympathetic nerves; excitatory effects are produced by the intact ergone; inhibitory effects by a degradation product called "adrenoxin."5

Because of discrepancies between these four theories, further studies were done in this laboratory to test their validity by comparing the responses of the blood vessels of skeletal muscle to lumbar sympathetic nerve stimulation with those to intra-arterial injection of l-epinephrine and l-norepinephrine. Such comparisons were made before and after progressively increasing levels of adrenergic blockade.

Methods

Twenty-seven successful experiments were performed on 30 random mongrel dogs of both sexes weighing, on an average, 13.0 Kg. In each the left lumbar sympathetic chain was exposed retroperitoneally and vessels of the left thigh muscles were cannulated for flow measurements according to the techniques described elsewhere.6 The rate of flow was measured with an electromagnetic flowmeter.7 Lateral pressure was recorded just downstream from the flowmeter by means of a Statham P-23A strain gauge and a Brush strain analyzer. The general techniques for anesthesia, anticoagulant, preparation of solutions, recording and calculations are given elsewhere.6 During each experiment the sympathetic chain was stimulated at each of the levels, L3, L4 and L5, with monophasic square-wave pulses at a rate of 20 per sec. The impulses (2–4 V; 15 m sec) were furnished by a Grass S 4 A stimulator. L-epinephrine and l-norepinephrine were given intra-arterially in doses of 1, 2, 3 and 10 agus. Atropine was given intra-arterially in doses of 0.01 to 0.04 mg. In each of the experiments a control series of intra-arterial injections of the adrenergic drugs and...
of stimulations at L5, L4 and L3 were given. The series of drug injections and stimulations was repeated after each of a series of progressively increasing doses of one of the adrenergic blocking agents. The blocking drugs used were phenoxybenzamine, azepetine, phentolamine, and tolazoline.* Each was given intra-arterially, in logarithmically increasing doses of 0.01, 0.03, 0.1, 0.3, 1.0, 3.0, 10.0 and 30.0 mg./Kg. Only one blocking drug was used in a given experiment. The structural formulae of these agents are given in a previous paper. Except as noted, the effects of all four were quite similar.

Since the stimulation was maintained over a period of 30 seconds to 2 minutes, the mediator would presumably be released continuously over this period of time. It was felt that there might be some differences in adrenergic response between such gradual release and the usual 1 to 4 sec. periods of drug injection. Therefore, in several experiments we compared the responses to slow uniform-rate injections with those to rapid injections of the adrenergic drugs.

RESULTS

I. Methods of Presenting Data. The following abbreviations are used throughout the presentation: EPI for 1-epinephrine, NOR for l-norepinephrine, and NERVE for lumbar sympathetic nerve stimulation. Original records of the flow responses to NERVE at L5 and to EPI and NOR in the control state and after a moderately large dose of phenoxybenzamine are reproduced in figures 1 to 4. Figures 5 to 7 give the means and standard errors of all of the changes in resistance in the control state (dose 0.0) and after each of the doses of phenoxybenzamine, in all of the experiments in which this blocking drug was used.

II. Control Data. The blood flows before the injection of any drug ranged from 7.4 to 85.0 with an average of 24.72 ml./min.; mean arterial pressure ranged from 38 to 148 with an average of 108.2 mm. Hg; and the resistances ranged from 1.40 to 12.54 with a mean of 6.02 PRU.

III. Control Responses

A. Lumbar sympathetic nerve stimulation. In the control phase of the experiments NERVE at L5 caused a primary vasoconstriction in 67 per cent of all stimulations (Type I response,
Fig. 2. Records of typical blood flow responses to 10 μg.m. of L-norepinephrine (7, 18) and to lumbar sympathetic nerve stimulation (39) during the control state. See legend for fig. 1 for further details. Same experiment as fig. 1.

Fig. 3. Records of responses of blood flow and arterial pressure to 10 μg.m. of L-epinephrine and L-norepinephrine and to lumbar sympathetic nerve stimulation at L5 (46) after an intra-arterial injection of 0.3 mg/Kg. of phenoxybenzamine. Pressure records for (44) and (46) are so marked. Numbers adjacent to the pressure tracing are mean perfusion pressures in mm. Hg. In record 43 the symbols 50% and 25% indicate a change in the sensitivity of the recorder from 50 to 25% of maximum sensitivity; conversely, in Record 44 the sensitivity was restored to 50 per cent of maximum. Slow-speed recordings indicated by symbol U accompanying the numbers 5', 158' give duration of the slow-speed recording. For other details see legends for Fig. 1. Same experiment as fig. 1.
fig. 1, record 34). In 20 per cent of all stimulations at L5, there was a brief period of primary vasodilation followed by a period of vasoconstriction which lasted as long as the stimulus was applied, (Type II response, fig. 2, record 39). In 13 per cent of all stimulations at L5, only vasodilation occurred (Type III response, similar to fig. 3, flow record 46). The responses at L4 and L3 were similar; in general the magnitudes of the vasoconstrictor responses were greatest at L5, less at L4 and least at L3 (fig. 5, dose, 0.0).

Secondary vasodilation following the period of vasoconstriction (fig. 1, record 34) was present in 20 per cent of all stimulations (fig. 2, record 39). When present, it was of smaller mean magnitude (fig. 5, dose 0.0) than that following the vasoconstrictor phase of either NOR (fig. 6, dose 0.0) or EPI (fig. 7, dose 0.0). There was no correlation between the level at which the sympathetic chain was stimulated and whether or not secondary vasodilation occurred. The magnitude of the secondary vasodilator response was not related in any way to the magnitude of the preceding vasoconstriction, nor was the magnitude of the vasoconstriction related in any way to whether or nor vasodilation followed. No correlation was observed between the condition of the animal and the type of response.
Fig. 5. Plots of the mean responses in all experiments to lumbar sympathetic nerve stimulation (STIM) at L5, L4 and L3, in per cent of control resistance (PRU) (ordinate scale). Control state at 0.0 on abscissa; increasing levels of adrenergic blockade at points 0.01, 0.03, 0.1, etc. Dose of phenoxybenzamine in mg./Kg. given before stimulation also shown. Vertical bars indicate ±1 standard error from the mean. Upper solid lines, constrictor responses; lower solid lines, dilator responses; broken lines, mean initial constrictor or dilator responses. Deviation of broken lines away from the upper towards lower solid line indicates degree of "reversal" of primary constrictor responses.

B. L-norepinephrine. Response to control injections of NOR resembled closely those to nerve stimulation. The principal differences were: (a) Control injections of 1 μgm. NOR caused slightly more vasoconstriction than stimulation at L5 and progressively greater vasoconstriction resulted from the 3 and 10 μgm injections. (b) Secondary vasodilation remained about the same for all doses and, in each instance, was greater than that for NERVE. (c) Type III responses were entirely absent. Some Type II responses were seen but less frequently than with NERVE.

C. L-epinephrine. Responses to EPI differed from those to NOR and NERVE in the following respects: (a) Injections of 1 μgm. EPI caused slightly more vasoconstriction than NERVE but less than that caused by 1 μgm. NOR. (b) EPI caused much more secondary vasodilation than comparable injections of NOR and very much more than NERVE. (c) Both vasoconstriction and secondary vasodilation increased with progressively increasing doses of EPI (fig. 7, dose 0.0).

D. Responses to slow injections. In general, slow injections of 1, 3 and 10 μgm. of EPI and NOR all gave slightly less constriction and slightly more secondary dilatation than did comparable doses that were injected rapidly.

IV. Effects of Adrenergic Blockade with Phenoxybenzamine

A. Lumbar sympathetic nerve stimulation. The first significant effect of phenoxybenzamine blockade was noted at 0.03 mg./kg. which was a considerable reduction in the magnitudes of the vasoconstrictor responses to stimulation at L4 and L3, a small reduction of the responses to stimulation at L5 (fig. 5, dose 0.03), and an increase in the number of Type III responses to stimulation at L4 (mean response shown by broken line just below line "L4 Stimulation"). No significant change in secondary vasodilation was noted.

Further increase in the dose of phenoxybenzamine was without significant effect on NERVE responses until the 0.3 mg./kg. dose level was reached when there occurred a considerable reduction in magnitude of Type I responses, and an increase in number of Type III responses to stimulation at L5.

Phenoxybenzamine, 1.0 mg./kg., further reduced the magnitude of the L5 Type I responses and slightly increased the incidence of
Type III responses (fig. 5, dose 1.0). When L3 secondary vasodilator responses occurred they showed some increase in magnitude, and the mean primary response to stimulation at L3 and L4 became Type III in nature.

With 3.0 mg./kg. phenoxybenzamine, the only remarkable change consisted in some reduction in the magnitude of the secondary vasodilation for stimulation of L5, L4, and L3, and a small reduction in Type III responses for stimulation at L4.

Phenoxybenzamine, 10.0 mg./kg., abolished all responses except a slight vasoconstrictor response to stimulation at L5 (112 per cent of control PRU).

Nowhere in figure 5 does the mean response to stimulation at L5 become vasodilator in nature; it remains vasoconstrictor throughout. In general, the vasoconstrictor responses to stimulation at L4 and L3 were more readily blocked than those at L5.

B. L-norepinephrine. The NOR responses during blockade were essentially the same as those discussed by Lanier et al (6) and by Johnson et al (9). Smaller doses of the blocking drug were required to block vasoconstriction and unmask dilator responses (reversal) to 1 \( \mu \text{g} \) than to 3 and 10 \( \mu \text{g} \) doses of NOR. Larger doses of the blocking drug were required to block vasodilator responses to the larger doses of NOR. At the point of reversal, the magnitudes of the vasodilator responses were, in general, larger for the larger doses of NOR.

During adrenergic blockade, as well as during control studies, responses to NOR resembled closely those to NERVE (fig. 3, 5, and 6). For each: (a) Blockade of constriction began at 0.01 to 0.03 mg./kg. of phenoxybenzamine. (b) Constriction was reduced to approximately 120 per cent of control PRU at 0.3 mg./kg. (c) Secondary dilator responses were minimal at 0.03 to 0.1 mg./kg. (d) Primary dilator responses were maximal at approximately 1.0 mg./kg. (e) All dilator responses were abolished at 10.0 mg./kg.

The principal points of difference were: (a) The magnitude of the primary dilator response to 10 \( \mu \text{g} \) of NOR was greater after 1.0 mg./kg. phenoxybenzamine. (b) All constrictor responses to NOR were abolished with 1.0 to 3.0 mg./kg. phenoxybenzamine, whereas it required more than 10.0 mg./kg. to abolish completely the constrictor responses to NERVE.

C. L-epinephrine. The responses to EPI during adrenergic blockade were essentially the same as described in previous papers from this laboratory (6, 9). The larger doses (3 and 10 \( \mu \text{g} \)m.) of EPI were reversed and the constrictor and dilator responses were each blocked at approximately the same level as the 1 \( \mu \text{g} \)m. dose. In general, the magnitude of the reversal was greater for the larger doses of EPI (fig. 3 and 7).

The points of comparison and contrast between the responses to EPI, and those to NOR and NERVE noted during adrenergic blockade were: (a) Blockade of constriction and onset of reversal occurred with use of much smaller dose of phenoxybenzamine (0.03 to 0.1 mg./kg. for EPI, 0.3 to 1.0 mg./kg. for NOR, and 0.3 to 10.0 mg./kg. for NERVE). (b) The maximum dilator responses occurred at about the same level of blockade for all three (0.3 mg./kg. for EPI, 1.0 mg./kg. for NOR, and 0.3 to 1.0 mg./kg. for NERVE). (c) The maximum dilator responses were of much greater magnitude for EPI (20 to 23 per cent control PRU) than for NOR (51 to 80 per cent of control PRU), or for NERVE (72 to 85 per cent of control PRU). (d) The dilator responses were blocked at the same doses for EPI, NOR, and NERVE.

V. Responses During Blockade with Other Adrenergic Blocking Agents. The principal differences in the four blocking drugs were in the doses required to provide the various levels of blockade. These are reported elsewhere (10). The only significant differences in the responses elicited during blockade in comparison with phenoxybenzamine were: No marked secondary responses to NERVE were seen with any of the three; and primary vasodilation (reversal) in response to NOR was inconsistently seen during azapetine blockade and was almost completely absent during blockade with phentolamine and tolazoline.

VI. The Effects of Atropine Blockade on the Responses

A. Sympathetic nerve stimulation. The vasodilation seen in Type II responses to NERVE was abolished easily by the intra-arterial in-
jection of 0.01 to 0.04 mg. atropine sulfate in the control phase and at all levels of adrenergic blockade in experiments where this type of response occurred. The vasodilation seen in Type III responses was markedly reduced, abolished or converted into a vasoconstrictor response by the same doses of atropine both in the control phase and at all levels of adrenergic blockade in all experiments (fig. 3, record 46 and 4 record 58). It may be noted that the fluctuations in blood flow seen in fig. 4 record 58 are mere reflections of pressure changes seen in fig. 4 record 58 and do not represent any real change in PRU, as is also the case in fig. 3 record 46. This suggests that there are vasodilator nerves of a cholinergic nature in the sympathetic chain (see also 11). Unfortunately, in none of the experiments where atropine was used, were secondary dilator responses present.

B. L-norepinephrine. The effects of atropine on the responses to NOR were observed in 21 instances which were about equally distributed between the 1, 3, and 10 /igm. doses of NOR. In 6 of these, which were about equally distributed between the 3 dose levels of NOR, there was no effect. In 2, during phenoxybenzamine blockade, there was a slight decrease in constrictor response. In the remaining 11, of which 1 was during a control period, 1 during phentolamine blockade, 3 during aza-petine blockade and 3 during phenoxybenzamine blockade, there was an increase in the constrictor response and/or a reduction in the dilator response. This effect is illustrated in figures 3 and 4. In figure 3 the second rise in blood flow is accompanied by some rise in blood pressure but represents a true change in PRU, while in fig. 4 the second rise in blood flow merely accompanies the blood pressure rise, and is not a change of PRU. The sharp initial rise of blood flow was not accompanied by a pressure change and was not affected by atropine.

The above observations indicate that, in the vasculature of skeletal muscle, NOR stimulates vasodilator receptors which are capable of being blocked, at least partially, by atropine.

C. L-epinephrine. The effects of atropine on the responses to EPI were studied in 21 injections which were about equally distributed between the 1, 3, and 10 /igm. doses of EPI. In 14 of these, no effect was noted. In 2 of the 10 /igm. injections and in 1 of the 1 /igm. injections given during azapetine blockade, dilator responses were reduced and constrictor responses were increased. In the remaining four injections, of which 2 were during azapetine and 2 were during phenoxybenzamine blockade, there was a small decrease in constrictor and/or a slightly greater dilator response. We interpret these data as indicating that atropine has no effect on the vascular responses to EPI.

**GENERAL DISCUSSION**

A. Possible mediators for Vasoconstriction Induced by Lumbar Sympathetic Chain Nerve Fibers

1. Possibility that a substance different from both epinephrine and norepinephrine might be the mediator. In general, in the control period primary vasoconstriction was greatest for NOR, next for EPI, and least for NERVE. With all four blocking drugs, as blockade was increased progressively to moderate levels, NOR and NERVE responses remained similar, whereas the constrictor responses to EPI were abolished and replaced by marked dilator responses. With further increase in the level of blockade, the constrictor responses to NOR were abolished and, especially during phenoxybenzamine blockade, converted to a weak dilator response. Only at the highest levels of blockade were the constrictor responses to NERVE abolished, and at this level no significant dilator responses were noted. This comparison would seem to suggest that the neurohormone is neither NOR nor EPI, but that the nerve releases a different constrictor substance which is more resistant to blockade and which possesses less capacity to stimulate the beta receptor19 than either EPI or NOR. However, chemical evidence to date has demonstrated the presence only of EPI and/or NOR in autonomic nerve fibers.

2. Access to alpha receptors. A second possibility to account for the greater resistance to blockade of the constrictor response to NERVE is that the neurohormone has better access to the alpha receptors.19 This may well be the case for the nerve endings would be expected to be in close approximation to the smooth
muscle of the blood vessel wall and might therefore succeed in developing a relatively higher local concentration at the alpha receptor than could be obtained by intra-arterial injection.

c. Access to beta receptors. A third possibility is that the neurohormone has a less effective access to the beta receptor than does intra-arterially injected NOR or EPI. Mohne-Lundholm\textsuperscript{14} has suggested that the dilution induced by EPI results from lactic acid released by the breakdown of glycogen in the skeletal muscle. This would place the beta receptor within the skeletal muscle. If this is the case, then intra-arterially injected NOR and EPI could reach the beta receptor in high concentration relative to that at the alpha receptor. On the other hand the neurohormone, released only at the site of the alpha receptor, might be destroyed rapidly enough by the amine oxidase at this site that the concentration which would reach the beta receptors by diffusion would be quite small relative to that at the alpha receptor. This would result in there being very little or no vasodilation in response to nerve stimulation as compared to NOR and EPI.

d. Conclusion: Mediator is probably norepinephrine. If EPI, and especially NOR, weakly stimulates the beta receptors, and these receptors are more resistant than the alpha receptors to blockade, then the release of a dilator substance at the beta receptors could well over-ride the weak stimulation of the alpha receptors during partial blockade, thereby resulting in no response (apparent blockade of constriction). This could account for the smaller doses of the blocking drug required to block the constrictor response to NOR and especially to EPI, as compared to that of NERVE, which has little capacity to stimulate the dilator mechanism. On this basis, the neurohormone may very well be NOR, which, being released in localized quantities at the alpha receptor, resists blockade and at the same time does not diffuse sufficiently to stimulate vasodilation at the beta receptors.

If, as von Euler\textsuperscript{14} and Tainter and Luduena\textsuperscript{14} have suggested, both EPI and NOR are liberated by NERVE, then it would seem most reasonable to expect a greater secondary vasodilation following NERVE than that seen following an injection of NOR, because of the greater effect of EPI on the beta receptors. Our results indicate that, if EPI is present in the neurohormone, it is in such small amounts that its physiological action cannot be detected by our methods.

B. Mediator for Vasodilation Induced by Lumbar Sympathetic Chain Nerve Fibers.

a. Evidence that mediator is cholinergic. Primary vasodilator responses to NERVE were initially present in many of the experiments. At increasing levels of adrenergic blockade, they became more prominent and numerous as the constrictor effect of NERVE was eliminated. Atropine readily blocked all of these primary dilator responses both in the control phase and during adrenergic blockade. This observation confirms the reports of Folkow and Uvnäs\textsuperscript{11, 12}, and suggests that there are cholinergically mediated vasodilator fibers in the sympathetic chain.

b. Evidence that mediator might be norepinephrine. Atropine had no effect on constriction or primary and secondary dilator responses to EPI, either before or during adrenergic blockade. This finding supports the observations of Hunt, Bulbring and Burn, Wyman and tum Suden (for references see\textsuperscript{14}), and Uvnäs\textsuperscript{17}. On the other hand, atropine tended to augment the constrictor responses and to reduce the dilator responses to NOR, particularly during adrenergic blockade. Evidently NOR weakly stimulates dilator receptors in the vasculature of skeletal muscle which are to some extent susceptible to blockade by atropine. This blockade occurred simultaneously with, though less consistently than, blockade of dilator responses to NERVE. In view of these observations, it appears that either atropine exerts a weak blocking action on the beta receptors or NOR weakly stimulates the cholinergic vasodilator mechanism.

SUMMARY AND CONCLUSIONS

Principal theories concerning the nature of the adrenergic nerve mediator have been stated briefly. To test these theories we have measured simultaneously the changes in arterial
pressure and blood flow in the skeletal muscle vascular bed of the dog's hind limb during stimulation of the lumbar sympathetic nerves at L5, L4 and L3, and during intra-arterial injections of 1, 3 and 10 μg of 1-epinephrine and of l-norepinephrine, both in the control state and at progressively increasing levels of adrenergic blockade.

Nerve stimulation, caused constriction, or dilation followed by constriction, in the control phase. The constrictor responses were abolished by the adrenergic blocking drug with simultaneous appearance of, or augmentation of pre-existing, vasodilator responses. Atropine readily abolished all dilator responses.

L-norepinephrine caused vasoconstriction with secondary dilation in the control phase. The adrenergic blocking drugs reduced, and with larger doses abolished, the constrictor and secondary dilator responses. With Dibenzyline, moderate primary dilator responses were unmasked. Atropine frequently reduced and occasionally almost completely abolished these primary dilator responses. They were abolished also by still larger doses of the adrenergic blocking drugs.

Epinephrine caused constriction followed by dilation in the control phase. The adrenergic blocking drugs readily abolished the constrictor and unmasked marked primary dilator responses. The dilator responses were abolished only with the largest doses of the adrenergic blocking drugs. Neither the constrictor nor the dilator responses were affected appreciably by atropine.

There are probably three vasoactive mechanisms in skeletal muscle which respond to autonomic stimulation:

(a) An adrenergic vasoconstrictor mechanism (alpha receptor) which is stimulated strongly by l-epinephrine, l-norepinephrine and by sympathetic nerve impulses. The last are probably mediated by l-norepinephrine; the sensitivity of this receptor is reduced by moderate and abolished by high doses of adrenergic blocking drugs, but it is unaffected by atropine.

(b) An adrenergic vasodilator mechanism (beta receptor) which is stimulated strongly by isopropylnorepinephrine (Green and co-workers\textsuperscript{8}, and l-epinephrine and slightly by l-norepinephrine; the sensitivity of this receptor is not affected by atropine but is blocked at about the same dose of adrenergic blocking drugs as (a).

(c) Another vasodilator mechanism (gamma receptor) which is capable of being stimulated by nerves lying in the lumbar sympathetic chain and by methacholine and probably moderately by l-norepinephrine; the response to the nerve impulses is probably mediated cholinergically; the sensitivity of this receptor is readily abolished by atropine and by very high levels of adrenergic blocking drugs.

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