JCI The Journal of Clinical Investigation

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J Clin Invest. 1969;48(7):1328-1335. https://doi.org/10.1172/JCI106099.

Research Article

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Beta-Receptor Mechanisms in the Superficial Limb Veins of the Dog

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ABSTRACT The lateral saphenous vein of dogs was perfused at constant flow with autologous arterial blood, and perfusion and femoral vein pressures were monitored; changes in the difference between these pressures were due to changes in venomotor activity. Injection of isoproterenol into the perfusate caused the vein to dilate. The amount of dilatation depended on smooth muscle tension in the wall of the vein before injection. When this was minimal (after sympathectomy), isoproterenol had no effect. During venoconstriction produced by electrical stimulation of the lumbar sympathetic chain or by the infusion of venoconstrictor drugs, the dilating action of 0.1 mg of isoproterenol was measured. Expressed as a percentage of the initial constriction caused by sympathetic stimulation, 5-hydroxytryptamine, or 1 M potassium chloride, the extent of the dilatation was 86.7 ±4.3 (SE of mean), 79.7 ±4.2, and 87.7 ±3.2, respectively. With norepinephrine and epinephrine infusions, the isoproterenol dilatations were less (65.1 ±9.0 and 55.2 ±7.2, respectively), consistent with the stimulant action of these agents on both alpha and beta receptors; such action was confirmed by comparing the responses to nerve stimulation and infusions of norepinephrine and epinephrine before and after beta-receptor blockade. The venoconstriction caused by sympathetic stimulation and by infusions of norepinephrine and epinephrine was greatly enhanced by cooling the vein (decreasing perfusate temperature), but the dilating action of isoproterenol appeared to be insensitive to changes in temperature. The data suggest that beta receptors are specific entities and, when maximally stimulated, are capable of causing a venous relaxation that is proportional to the initial degree of tension in the vein wall.

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Received for publication 23 July 1968 and in revised form 24 February 1969.

INTRODUCTION

The role of beta receptors in the venous system is controversial. Folkow (1) found that isoproterenol caused more dilatation of resistance vessels than of capacity vessels in skinned hind limbs of cats, but Kaiser, Ross, and Braunwald (2), using a heart-lung bypass preparation, reported constriction of the "over-all" venous bed in the dog after systemic administration of the drug before and after ganglionic blockade. More recently, Abboud, Eckstein, and Zimmerman (3) and Zsoter and Tom (4) concluded that, in the limb veins of dogs and cats, beta-receptor stimulation results in dilatation, but the venodilator response is small. In man, the forearm veins show slight (5) or no dilatation (6) when isoproterenol is given into the brachial artery, but constriction of forearm veins has been reported with systemic administration of large doses (7). Isoproterenol has also been shown to cause relaxation of isolated strips of smooth muscle from the portal vein of rat (8) and rabbit (9).

In the present experiments, the responses of the lateral saphenous vein of the dog to direct injection or infusion of isoproterenol were studied. The results indicate that beta receptor stimulation causes venodilatation, the magnitude of which is proportional to the initial smooth muscle tension in the vein wall.

METHODS

Mongrel dogs weighing 15–25 kg were anesthetized with thiopental (15 mg/kg intravenously) and chloralose (80 mg/kg intravenously) and ventilated artificially with oxygen. The left lateral saphenous vein was cannulated at the ankle and perfused at constant flow (roller pump; flow rate, 100 ml/min) with blood taken from the median sacral artery. A heat exchanger was placed in the circuit, and perfusion and femoral vein pressures were measured. During experiments, the left common iliac artery was occluded. Previous analysis of the method (10) has shown that, after cannulation of the median sacral artery and occlusion of the common iliac artery, the blood flowing into the venous tree

of the leg under study is supplied solely by the constant flow roller pump. Hence, any change in the difference between perfusion (inflow) and femoral vein (outflow) pressures is due to a change in the venomotor activity of the lateral saphenous vein.

The drugs used in the study were isoproterenol hydrochloride (Isuprel), *l*-norepinephrine bitartrate (Levophed), epinephrine chloride (Adrenalin chloride), 5-hydroxytryptamine (serotonin creatinine sulfate, Abbott Laboratories, North Chicago, Ill.), propranolol (Inderal), and potassium chloride (75 g/liter in isotonic saline). Fresh dilutions in isotonic saline were prepared for each experiment. The doses of norepinephrine are given in terms of the free base. The doses of all other agents are expressed in terms of their salts. All test drugs were infused or injected upstream from the roller pump to ensure adequate mixing.

Lumbar sympathectomy. The left lumbar sympathetic trunk was divided at the level of the second or third lumbar vertebral body and dissected free down to the level of the sixth lumbar vertebral body. The sympathetic fibers to the veins of the hind limb leave the spinal cord in the first to fourth lumbar nerves, run in the main sympathetic trunk from the third to the sixth lumbar ganglion, and leave the sympathetic trunk to join the sciatic nerve by the rami to the sixth and seventh lumbar and first and second sacral nerves (11, 12). This procedure should therefore have interrupted the venomotor fibers that traverse the sympathetic trunk. The completeness of sympathectomy was confirmed by the absence of changes in venomotor tone when the temperature of the blood perfusing the vein was changed, because it has been shown that the powerful venoconstriction that is normally seen on cooling the perfusate is dependent on an intact autonomic nerve supply to the vein (13, 14).

Lumbar sympathetic nerve stimulation. The distal end of the divided lumbar sympathetic trunk was stimulated at the level of the fourth or fifth lumbar vertebral body, via a

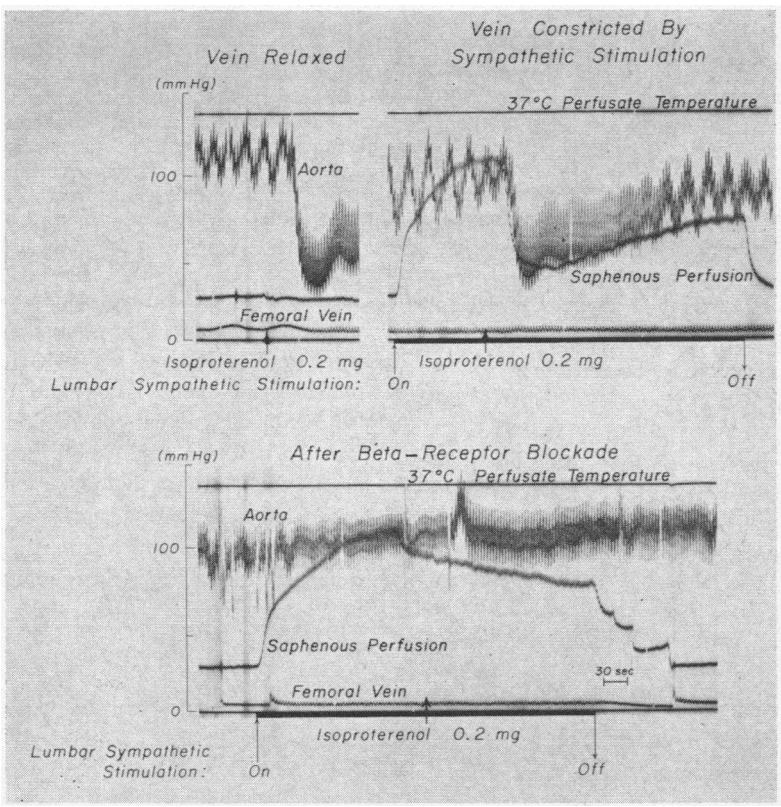

FIGURE 1 Effect of changes in venomotor tone, induced by electrical stimulation of lumbar sympathetic chain, on response of lateral saphenous vein to isoproterenol (0.2 mg injected into venous perfusate). Scale at left refers to aortic, saphenous perfusion and femoral vein pressures. Upper left: after lumbar sympathectomy, venomotor tone is minimal (perfusion pressure, second tracing from bottom of 30 mm Hg) and is unaffected by isoproterenol, although aortic pressure decreases sharply. Upper right: when venoconstriction is induced by electrical stimulation of lumbar sympathetic chain (first signal) at rate of 4 cps, same dose of isoproterenol (second signal) produces profound venodilatation shortly before decrease in aortic pressure. Lower: after infusion of propranolol to block beta receptors, profound venodilatation is abolished. Gradual decrease in saphenous perfusion pressure may be attributed to fatigue caused by long duration of lumbar sympathetic stimulation.

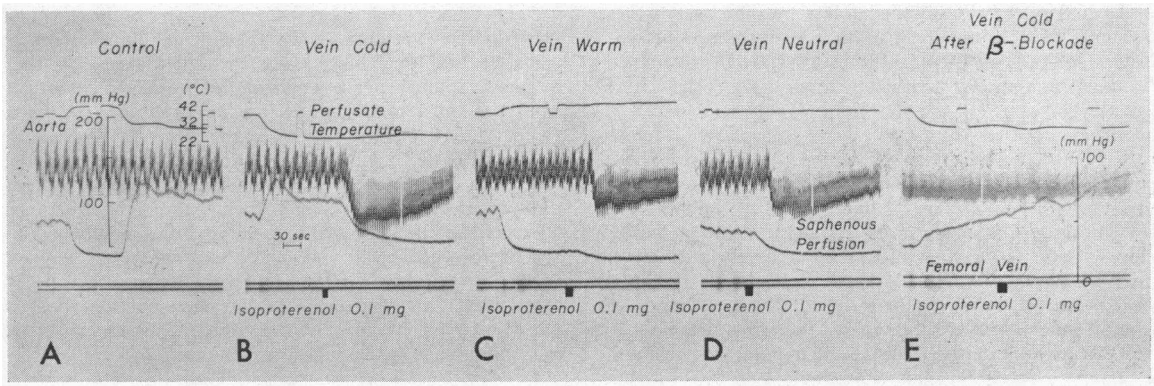

FIGURE 2 Effect of changes in venomotor tone, induced by alterations in venous perfusate temperature (scale marked °C), on response of lateral saphenous vein to isoproterenol (0.1 mg injected into venous perfusate). Scale at left refers to aortic pressure; scale at right to saphenous perfusion and femoral vein pressures. Square wave deflections in perfusate temperature tracing are due to temporary switching of galvanometer to read esophageal temperature. A: effect of changes in venous perfusate temperature on venomotor tone. Cooling perfusate causes constriction (increase in difference between venous perfusion and femoral vein pressures), whereas warming perfusate has opposite effect. B: effect of isoproterenol on venomotor tone after venoconstriction induced by cooling venous perfusate from 37 to 24°C. C: effect of isoproterenol on venomotor tone after venodilatation induced by warming venous perfusate from 37 to 42°C. D: effect of isoproterenol on venomotor tone at perfusate temperature of 37°C. E: after beta-receptor blockade, isoproternol did not affect the progressive venoconstriction induced by cooling the venous perfusate from 37 to 27°C.

platinum bipolar electrode, with a Grass Instrument Company stimulator (model S 4). A stimulus of 8 v (supramaximal) was applied for 1 msec with no delay at frequencies varying from 2 to 10 cycles/sec.

RESULTS

Preliminary experiments showed that, after left lumbar sympathectomy, when smooth muscle tension in the left saphenous vein wall was minimal, the injection of isoproterenol into the venous perfusate had no effect on the vein, although aortic pressure decreased sharply as a consequence of the dilator effect of isoproterenol on the resistance vessels (Fig. 1, upper left). When venoconstriction was induced by electrical stimulation of the lumbar sympathetic trunk and the same dose of isoproterenol was given, a profound venodilatation lasting from 7 to 10 min resulted (Fig. 1, upper right) shortly before the decrease in aortic pressure. After beta-receptor blockade with propranolol (30 mg in 30 ml of isotonic saline infused intravenously over 10 min), isoproterenol administered during lumbar sympathetic stimu-

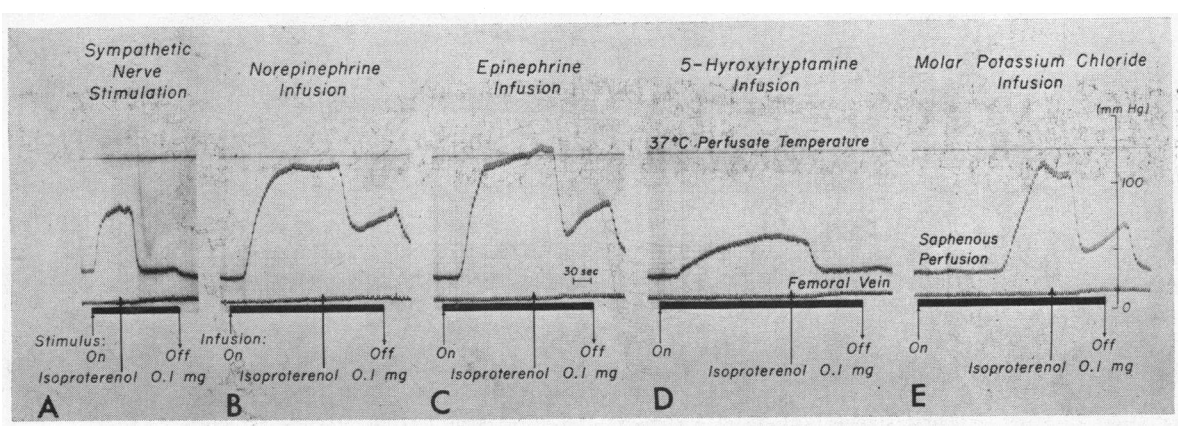

FIGURE 3 Effect of isoproterenol (0.1 mg injected into venous perfusate) on venomotor tone after venoconstriction induced in same dog by various stimuli. A: lumbar sympathetic stimulation (4 cps). B: infusion of norepinephrine (20 μg/min). C: infusion of epinephrine (20 μg/min). D: infusion of 5-hydroxytryptamine (50 μg/min). E: infusion of 1 M potassium chloride (4.94 ml/min).

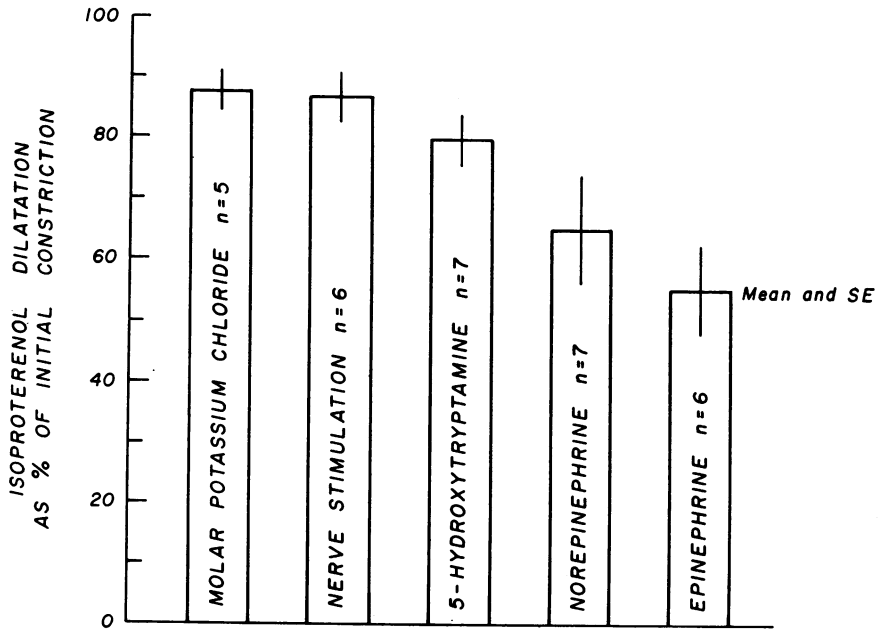

FIGURE 4 Effect of isoproterenol injection (0.1 mg) on venoconstrictor responses to various stimuli (n = number of dogs). On basis of two-tailed t test of significance on unpaired samples, significant differences were: KCl vs. norepinephrine, $P < 0.05$; KCl vs. epinephrine, $P < 0.01$; nerve stimulation vs. norepinephrine, $P < 0.05$; nerve stimulation vs. epinephrine, $P < 0.01$; 5-hydroxytryptamine vs. epinephrine, $P < 0.01$.

lation had no significant effect on either the venous perfusion pressure or the aortic pressure (Fig. 1, lower), indicating that the venodilatation seen in the previous experiment was the result of beta-receptor stimulation.

Changes in local venous perfusate temperature and in central body temperature have been shown to have a profound effect on venomotor tone in the lateral saphenous vein when the lumbar sympathetic chain is intact (13–15). By adjusting temperature conditions appropriately, it was possible to examine the effect of isoproterenol injections (0.1 mg) with the vein constricted, moderately constricted, and dilated (Fig. 2).

These preliminary experiments suggested that the degree of dilatation produced by the same dose of isoproterenol was proportional to the muscle tension in the vein wall before injection.

In the first of the main series of experiments, venoconstriction was induced by (*a*) electrical stimulation of the lumbar sympathetic trunk (six experiments), (*b*) infusion of norepinephrine (seven experiments), (*c*) infusion of epinephrine (six experiments), (*d*) infusion of 5-hydroxytryptamine (seven experiments), and (*e*) infusion of potassium chloride (five experiments). In each experiment, when a steady venoconstrictor state had been achieved (that is, when the saphenous vein perfusion pressure achieved a plateau after its initial increase), 0.1 mg of isoproterenol was injected into the venous perfusate. These experiments were all conducted at a perfusate temperature of 37°C. The absolute magnitude of the constrictor responses to nerve stimulation and to each of the four constrictor agents varied widely. Similarly, the absolute magnitude of the venodilatation produced by 0.1 mg of isoproterenol varied widely (Fig. 3). Control injections of saline were without effect. When the dilatation produced by isoproterenol (decrease in saphenous vein perfusion pressure gradient) was expressed as a percentage of the initial venoconstriction (initial increase in saphenous vein perfusion pressure gradient), it was apparent that isoproterenol produced a relatively consistent percentage dilatation with each method of inducing venoconstriction (Fig. 4). The effects of beta-receptor stimulation by isoproterenol did not differ significantly when the initial venoconstriction was due to nerve stimulation, infusion of potassium chloride, or infusion of 5-hydroxytryptamine. With norepinephrine and epinephrine, however, the percentage dilatations due to isoproterenol were significantly less (Fig. 4).

In a second series of experiments, isoproterenol was infused at a rate of 40 μg/min during maximal venoconstriction induced either (*a*) by stimulation of the lumbar sympathetic nerves at a frequency of 10 cps (five experiments) or (*b*) by norepinephrine infused at a high dosage (four experiments). The results are given

in Fig. 5. Again, the mean percentage dilatation due to beta-receptor stimulation was significantly less with norepinephrine than with nerve stimulation ($P < 0.01$).

Large doses of isoproterenol were used in these series of experiments to obtain maximal stimulation of the beta receptors. When the lateral saphenous vein is caused to constrict by stimulation of the lumbar sympathetic nerves or by infusion of 5-hydroxytryptamine, the dilatation caused by isoproterenol is dose dependent, and relaxation of the vein can be demonstrated with small doses. In two experiments in which the sympathetic nerves were stimulated at 2 cps and in two in which a comparable degree of venoconstriction was caused by an infusion of 5-hydroxytryptamine (1 μg/kg per min), isoproterenol injected in doses of 4, 13, and 23 μg caused a venodilatation which averaged 32, 60, and 79%, respectively, of the constriction caused by nerve stimulation and 5-hydroxytryptamine.

Previous studies had demonstrated that a decrease in the temperature of the blood perfusing the lateral saphenous vein greatly enhanced the response to nerve stimulation and norepinephrine (14). A third series of experiments was therefore conducted to determine if the venodilatation responses to isoproterenol were also temperature sensitive. The effect of injection of 0.1 mg of isoproterenol on the venoconstrictor response to stimulation of the lumbar sympathetic nerve was compared in four dogs at venous perfusate temperatures of 37 and 27°C. In the first animal, the same frequency of stimulation was used at both temperatures, with the result that a greater venoconstrictor response occurred at the lower temperature. In the remaining three dogs the frequency of stimulation was adjusted to give approximately equal responses at both temperatures. A similar experiment was performed in five dogs with norepinephrine infusion. The same dose of norepinephrine was used at both temperatures in the first animal, and again a much larger constrictor response was seen at the lower temperature. Thereafter the dose of norepinephrine was adjusted to give similar degrees of constriction at both temperatures. The effect of isoproterenol on the constrictor response to epinephrine also was investigated at perfusate temperatures of 27 and 37°C in four dogs. Again, cooling the vein was found to enhance its constrictor response to epinephrine; in all these experiments the dose of epinephrine was adjusted to give approximately equal constrictor responses at both temperatures. The results (Fig. 6) show that temperature had no significant effect on the dilator responses to isoproterenol.

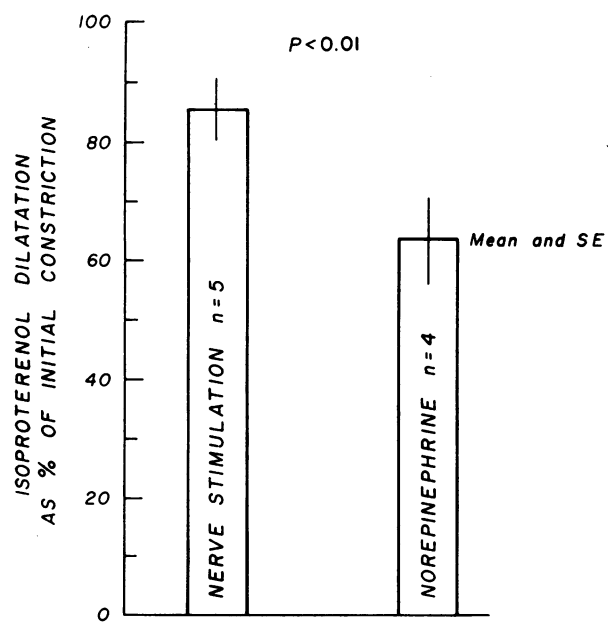

FIGURE 5 Effect of isoproterenol infusion (40 μg/min) on venoconstrictor response to electrical stimulation of lumbar sympathetic chain and to norepinephrine infusion (n = number of dogs).

Finally, the effect of beta-receptor blockade by propranolol (30 mg in 30 ml of isotonic saline infused into the left lateral saphenous vein over 10 min) on the venous responses to sympathetic nerve stimulation (10 cps) and to infusions of norepinephrine (20 μg/min) and epinephrine (20 μg/min) was investigated in four dogs (Fig. 7). After beta-receptor blockade, the responses to nerve stimulation were, if anything, slightly reduced, whereas the constrictor responses to norepinephrine and epinephrine were enhanced, more so to the latter.

DISCUSSION

The observation that the venodilatation consequent upon beta-receptor stimulation is proportional to the initial degree of venous tone may explain some of the contradictory findings in the literature. Under comfortable environmental conditions there is little activity in the nerve fibers to the human limb veins (16). The tone of the smooth muscle in their walls is at a minimum and, as a result, beta-receptor stimulation can only result in slight (5) or no dilatation (6). In the intact resting organism, the resistance vessels possess considerable resting tone, much of it intrinsic (myogenic) rather than neurogenic. By contrast, the veins are more dominated by the extrinsic nerve supply and possess little or no intrinsic tone (17). The observation that intra-arterial injection of isoproterenol caused more dilatation of resistance than of capacity vessels in the skinned hind limbs of cats (1) and in the forelimb (3) and hind limb (4) of dogs may merely be a reflection of the greater "resting" tone in the resistance as compared to the capacity vessels. Our results indicate that, in the presence

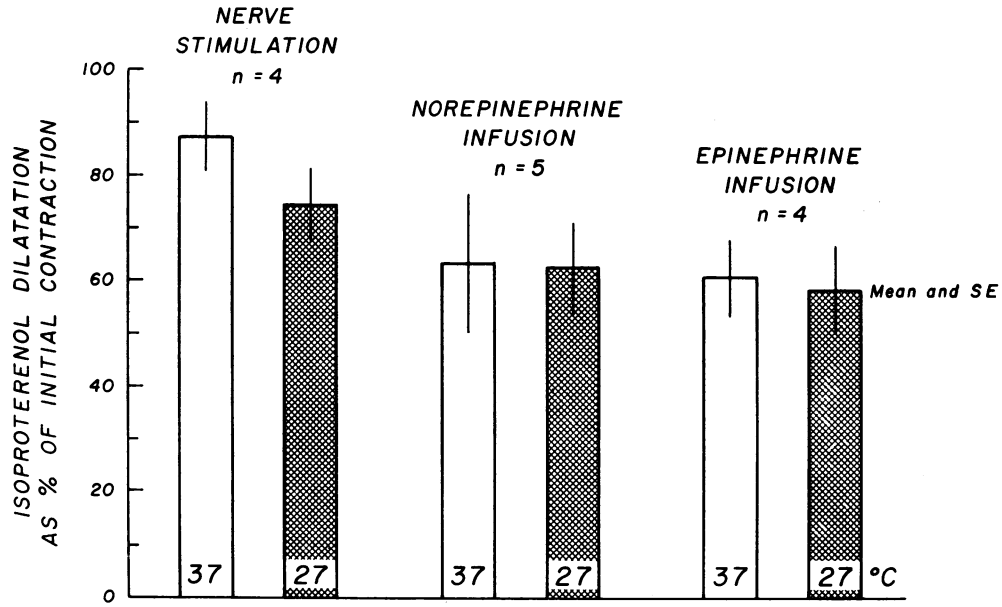

FIGURE 6 Effect of isoproterenol injection (0.1 mg) on venoconstrictor responses to electrical stimulation of lumbar sympathetic chain, norepinephrine infusion, and epinephrine infusion at perfusate temperatures of 37 and 27°C (n = number of dogs).

of a high initial venous tone, isoproterenol can exert a very powerful dilator action. Thus, it may not be possible to draw valid conclusions as to relative numbers or potency of beta receptors from absolute measurements of the dilatation induced by isoproterenol. Abboud, Eckstein, and Zimmerman (3) also noted that in the forelimb veins of the dog the venodilator responses to intra-arterial injection of isoproterenol were enhanced when the drug was given in the presence of a venoconstriction induced by infusions of norepinephrine.

The similarity among the percentage dilatations produced by isoproterenol in veins constricted by nerve stimulation, 5-hydroxytryptamine infusion, and potassium chloride infusion suggests that (*a*) the dilator beta-receptor mechanism is a distinct mechanism and not the result of competitive inhibition occurring at the alpha-receptor site and (*b*) the inhibition of tension by isoproterenol probably cannot be ascribed to an effect on membrane electrical activity, because the venoconstriction with potassium chloride presumably occurred with the smooth muscle in a depolarized state. Our in vivo results are in keeping with the observations by Johansson, Johsson, Axelsson, and Wahlström (8) who showed that, in the isolated rat portal vein, contracture tension produced by high extracellular potassium concentrations was reduced by isoproterenol without changes in membrane potential.

That the beta-receptor dilator mechanism is a discrete entity is also suggested by the experiments which examined the effect of temperature on the dilator responses to isoproterenol. The venoconstriction produced by nerve stimulation and by infusions of norepinephrine (14) or epinephrine was greatly influenced by changes in temperature: cooling augmented the response of the smooth muscle of the lateral saphenous vein, and warming had the reverse effect. By contrast, the dilator responses to isoproterenol injection seemed little affected by a 10°C decrease in temperature of the blood perfusing the vein.

The significant reduction in dilator effect of isoproterenol when the initial constriction was due to norepinephrine or epinephrine, in contrast to its effect when the constriction was due to nerve stimulation or infusion of 5-hydroxytryptamine or potassium chloride, is explained by the fact that epinephrine and norepinephrine have a weak beta-receptor action in addition to their alpha-receptor constrictor effect. Thus, fewer beta-receptor sites were available to the injected isoproterenol, with the result that the percentage dilatation with isoproterenol was less than when the initial constriction was the result of an agent having no stimulating action on the beta receptors.

A similar argument has been applied in reverse to explain the observation that, in the human forearm (18) and in the canine hind limb (19), epinephrine given intra-arterially normally evokes a vasodilator response in the resistance vessels whereas, if it is administered during infusion of isoproterenol, constriction of the resistance vessels is seen. Thus, if it is assumed that isoproterenol ocupies the beta receptors, when epi-

nephrine (which normally has a predominantly beta-receptor dilator effect on the resistance vessels in muscle) is subsequently given, only alpha receptors are available for attack, and the result is an unmasking of the weak alpha-receptor constrictor action of epinephrine.

By examining the effect of beta-receptor blockade on the responses of the lateral saphenous vein to nerve stimulation and to infusions of norepinephrine and epinephrine, we were able to test the hypothesis that, in the superficial limb veins, both norepinephrine and epinephrine have a beta-receptor dilator action in addition to their predominant alpha-receptor constrictor effect, whereas nerve stimulation results in pure alpha-receptor stimulation. In four dogs the responses to nerve stimulation were decreased, if anything, by beta-receptor blockade, whereas the responses to norepinephrine and epinephrine was significantly increased. This confirmed the indirect evidence from the previous experiments that nerve stimulation has a purely alpha-receptor constrictor effect, whereas direct infusions of norepinephrine or epinephrine result in stimulation of beta receptors in addition to their predominant alpha-receptor constrictor action. Both series of experiments suggested that epinephrine has a greater beta-receptor stimulating action than does norepinephrine but, in contrast to its effect on the arterioles in muscle, epinephrine has a marked constrictor action on the superficial limb veins, a finding indicating that in these vessels its alpha-receptor constrictor action strongly predominates over its beta-receptor dilator effect.

Glick, Epstein, Wechsler, and Braunwald (20) perfused (constant flow) the hind limbs and splanchnic vascular beds of the dog, and Brick, Hutchison, and Roddie (21) examined blood flow in the human forearm; both groups also concluded that norepinephrine released from nerve terminals in the arterial tree does not produce physiologically significant beta-receptor stimulation, but humorally transported norepinephrine stimulates both alpha and beta receptors.

ACKNOWLEDGMENT

This investigation was supported in part by research grant HE-5883 from the National Institutes of Health, U. S. Public Health Service.

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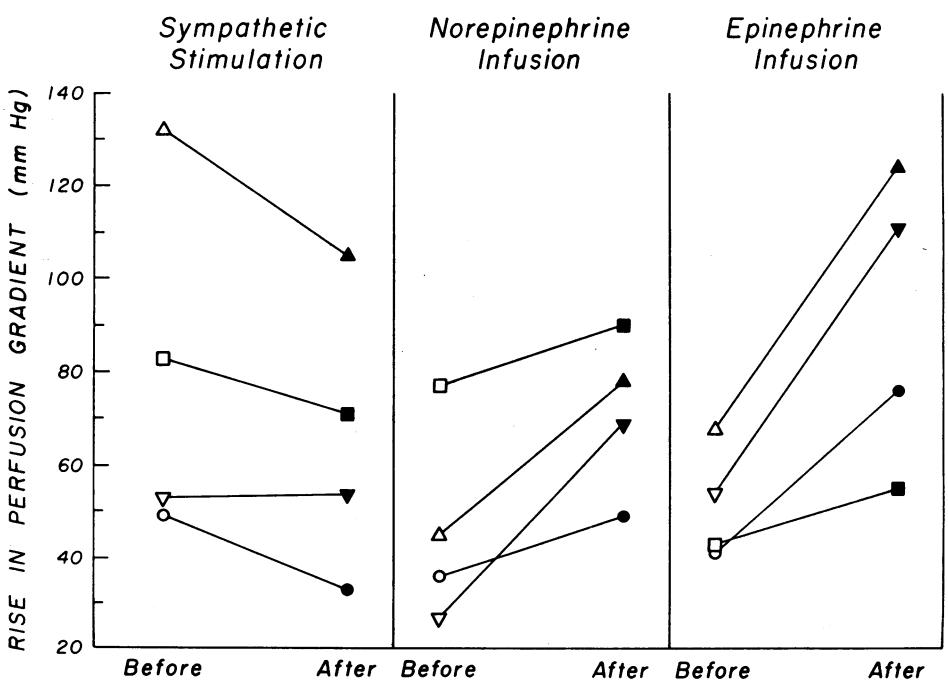

FIGURE 7 Effect of beta-receptor blockade on venomotor responses to sympathetic stimulation, infusion of norepinephrine, and infusion of epinephrine. Each symbol represents a different animal. Open symbols, before beta-receptor blockade; solid symbols, after blockade.

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