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SUMMARY Cardiac β-1 adrenoceptors respond to sympathetic nerve stimulation (SNS), but it is not clear that SNS evokes β-2 adrenoceptor-mediated vasodilation. Sensitivity of β adrenoceptors to catecholamines and to SNS was evaluated in dogs. Norepinephrine (NE) and epinephrine (E) were equipotent vasoconstrictors (femoral artery blood flow or gracilis autoperfusion pressure) before α-adrenoceptor blockade with dibozane (DIB). After DIB, NE was 1/100 as potent a vasodilator as E, which was equipotent with isoproterenol (ISO). SNS evoked gracilis muscle vasoconstriction before DIB and vasodilation after. Dilation induced by SNS or acetylcholine (ACH) after DIB was blocked by atropine (AT), but that caused by NE was not. Dilation evoked by NE, E, or I after DIB and AT was blocked by propranolol (PROP). Vasoconstrictor responses to NE, E, or SNS in dogs without DIB were not augmented by PROP at a dose that blocked the dilator effect of ISO. NE and E were equipotent and both 1/10 as potent as ISO as positive inotropic and chronotropic agents. Cardiac responses to NE, E, ISO, and SNS were antagonized by PROP. Subclassification of adrenoceptors that subserve cardiac stimulation as β-1 and that subserve vasodilation as β-2 was substantiated. Cardiac β-1 adrenoceptors responded to SNS and to circulating E and NE. Vascular β-2 adrenoceptors responded to circulating E, to ISO, and to high doses of NE, but not to SNS. β-2 Adrenoceptors in blood vessels appear not to be innervated and may function as hormone receptors sensitive primarily to E released from the adrenal medulla, rather than to NE released from adrenergic nerves. Circ Res 46: 344–352, 1980

β ADRENERGICALLY mediated vasodilation can be induced consistently by injections of isoproterenol or epinephrine after α-adrenoceptor blockade. However, there are conflicting reports regarding β adrenergically mediated vasodilation induced by sympathetic nerve stimulation. Some authors conclude that sympathetic nerve stimulation does elicit vasodilation independently from sympathetic cholinergically mediated vasodilation (Lundvall and Järhult, 1974, 1976; Pegram et al., 1976; Rengo et al., 1976; Tuttle and Moe, 1973; Viveros et al., 1968). One of the more widely quoted papers is that of Viveros et al. (1968) in which sympathetic nerve stimulation or norepinephrine given i.a causes vasodilation in the perfused gracilis muscle in dogs treated with dibozane and atropine.

However, other investigators have failed to identify such responses (Youmans et al., 1955; Glick et al., 1967; Rosell and Belfrage, 1975; Belfrage and Rosell, 1976; Folkow and Uvnäs, 1950; Dawes and Faulkner, 1975; Vatner and McRitchie, 1976). Youmans et al. (1955) suggested that the adrenoceptors (β-2 by modern terminology) are under only hormonal (epinephrine) control and do not respond to sympathetic nerve stimulation. They distinguished hormonal adrenergic vasodilation on the one hand from nerve-mediated adrenergic vasocontraction (α adrenoceptor) and sympathetic cholinergic vasodilation (muscarinic cholinceptors) on the other. This proposal was made 10 years prior to the sub-classification of adrenoceptors into β-1 and β-2 types by Lands and colleagues (1967). Glick et al. (1967) also concluded that norepinephrine released from sympathetic nerves stimulates only α adrenoceptors in vascular smooth muscle, and norepinephrine and epinephrine released elsewhere in the animal (i.e., from the adrenal gland) stimulate vascular β adrenoceptors. Rosell and Belfrage (1975) and Belfrage and Rosell (1976) stated that vascular α adrenoceptors are stimulated primarily by neuronally released norepinephrine and, therefore, could be considered as innervated receptors, but that vascular β adrenoceptors are unrelated to nerve terminals and are primarily stimulated by circulating catecholamines and thus are hormone receptors.

Norepinephrine is considered to be the sole neurohumoral mediator between postganglionic, adrenergic neurons, and effector cells (von Euler, 1956), even though it is a weak agonist on one subclass of...
adrenoceptors, i.e., β-2 type (Lands et al., 1967). In contrast, epinephrine is not considered to be a neurohumoral mediator in the mammalian sympathetic nervous system (von Euler, 1956), even though it is a potent agonist on α adrenoceptors as well as on both types of β adrenoceptors. The low potency of norepinephrine on β-2 adrenoceptor systems and the lack of consistent evidence for nerve-mediated, adrenergically induced responses through these receptors raises the possibility that β adrenergically induced vasodilation is only under hormonal control through adrenal medullary epinephrine, whereas adrenergically induced cardiac stimulation (β-1) and vasoconstriction (α) are under both hormonal (epinephrine and norepinephrine) and neurohumoral (norepinephrine) control.

The experiments described in this paper were designed to test the hypothesis that the β-2 adrenoceptors that subserve vasodilation in the gracilis muscle of the dog are not innervated.

Methods

General

Mongrel dogs (11-25 kg) of either sex were anesthetized by a mixture of pentobarbital (15 mg/kg, iv) and barbital (220 mg/kg, iv). An endotracheal tube provided a free airway. Body temperature, monitored with a thermistor probe in the thoracic esophagus, was maintained at 37-39°C by a circulating-water heating pad under the dog. Systemic arterial pressure was measured with a Statham P23AC pressure transducer connected to a plastic catheter in a brachial or femoral artery. A vein was cannulated for iv injections. All modalities were recorded on a Grass model 7 polygraph.

Experiments on Femoral Artery Blood Flow

These experiments were designed to verify the hypothesis that the β-2 adrenoceptors that subserve vasodilation as β-2 by assessing the order of potency of the three catecholamines, epinephrine, norepinephrine, and isoproterenol, as vasodilator agents and neurohumoral (norepinephrine) control.

The order of the injections was usually norepinephrine, isoproterenol, and then epinephrine. Sufficient time (5-10 minutes) was allowed between injections for pressure and flow to return to control levels. All ia injections were given rapidly in 0.1 ml of 0.9% saline and caused no change in arterial pressure. Intravenous injections were rapidly flushed in with 2-3 ml of isotonic saline. An α-adrenoceptor antagonist (either dibenamine, phentolamine, or phenoxybenzamine) next was administered by four slow iv infusions of 2, 4, 8, and 16 mg/kg, each infusion lasting 30-45 minutes and each providing a cumulative dose of 2, 6, 14, and 30 mg/kg. Between each dose of the α antagonist, iv injections of agonists were repeated as in the control period. However, only those results obtained in response to injections of agonists 10 or more minutes after the end of the final infusion of the α antagonist, dibenzamine, are given. Propranolol (1 mg/kg, iv) then was infused over a period of 20-30 minutes, and 10 minutes later, the agonists were given again.

Experiments in the Perfused Gracilis Muscle

The right gracilis muscle was prepared for perfusion from the left femoral artery by a modification of the method described by Viveros et al. (1968). The muscle was exposed through a skin incision and isolated from surrounding tissue. The femoral and gracilis arteries were isolated, and all branches were ligated. The gracilis and femoral veins were left in place. All other vessels supplying the gracilis muscle were ligated and cut, and the tendons at both ends of the muscle were tied in bundles. In sequence, the perfusion system consisted of: a polyethylene catheter directed centrally in the left femoral artery, Silastic tubing which passed through a peristaltic finger pump (Harvard Apparatus Co., model 600), a glass heat exchanger to maintain blood temperature at 37°C, Silastic tubing, a glass T-tube with a Statham P23AA pressure transducer connected to a side arm, a small length of latex tubing for ia injections, and finally a polyethylene catheter directed centrally in the right femoral artery below the origin of the gracilis artery. During the cannulation procedures, blood flow to the gracilis muscle was unimpaired. Heparin was administered (800 U/kg, initially; 400 U/kg, hourly). When the circuit was in place and had been primed with the dog’s blood, the perfusion pump was started, and the right femoral artery was occluded above the origin of the gracilis artery so that the entire perfusion of the gracilis muscle was through the extracorporeal system. The pump speed, adjusted so that perfusion pressure approximated arterial pressure, was held constant. (The pump delivered a constant flow over a range of 0-400 mm Hg pressure.) Twenty milliliters of dextran (Pharmacia, mol wt 77,500, 10 g/100 ml isotonic saline) were infused rapidly iv as soon as the perfusion system was established, and 80 ml were given later over a 10-minute period. Sympathetic nerves
to the muscle were stimulated either at the gracilis branch of the obturator nerve near the gracilis muscle or at the ipsilateral lumbar sympathetic chain.

Five types of experiments were performed on perfused gracilis muscles. Type 1 experiments were designed to demonstrate β adrenergically induced vasodilation and to establish the order of potency of the three catecholamines given ia, both before and after α-adrenoceptor blockade. The protocol for these experiments was similar to that used to study femoral artery blood flow. The gracilis muscle was denervated, and muncaric cholinergic blockade with atropine was maintained. Responses of systemic arterial pressure first were obtained to iv injections of agonists, and then responses of gracilis perfusion pressure were obtained to ia injections of agonists in 0.1 ml of 0.9% saline by schedules and doses described in Results. Next, the α-adrenoceptor blocking agent dibozane was administered slowly in divided doses, and after each dose, norepinephrine was injected iv and ia. Ten minutes after the final dose of dibozane was given (30 mg/kg cumulative) the agonists were injected iv and ia. When phentolamine and phenoxybenzamine were used (in one experiment each), the results were similar to those obtained with dibozane. Propranolol (1 mg/kg, iv) then was infused over a 20- to 30-minute period, and 10 minutes later, the agonists were repeated iv and ia.

Type 2 experiments were designed to compare the effects of injected catecholamines with those of lumbar sympathetic nerve stimulation. The right lumbar sympathetic chain was isolated by a transabdominal approach, the communicating rami cut at several levels, and the chain severed at L2. The chain at L3-L4 was placed on bipolar stainless steel electrodes. Responses of heart rate, right ventricular contractile force, and systemic arterial pressure were recorded in response to rapid iv injections of a wide range of doses of norepinephrine, epinephrine, tyramine, isoproterenol, and acetylcholine and to nerve stimulation before and after propranolol (1 mg/kg, iv) were studied.

Cardiac Experiments

Anesthetized dogs were artificially respired, the cervical vagus nerves cut, and the chest opened by a midsternal incision. A Walton-Brodie strain gauge arch was sutured to the right ventricle for recording isometric contractile force. The segment of myocardium between the feet of the arch was stretched approximately 50%. The right stellate ganglion was isolated, and all branches were cut except the ansa subclavia which was placed on bipolar, stainless steel electrodes. Responses of heart rate, right ventricular contractile force, and systemic arterial pressure were recorded in response to rapid iv injections of a wide range of doses of norepinephrine, epinephrine, and isoproterenol and to a wide range of frequencies of nerve stimulation. After these interventions, propranolol was administered slowly iv in five separate doses to reach a cumulative dose of 1 mg/kg. After each dose of propranolol, a single dose of norepinephrine, epinephrine, and isoproterenol and one frequency of nerve stimulation were repeated.

Drugs

The following drugs were purchased as commercially prepared solutions: 1-norepinephrine bitar-
Femoral Artery Blood Flow

In the control period, norepinephrine and epinephrine caused vasoconstriction (i.e., elevated arterial pressure with iv injection and decreased femoral artery blood flow with ia injection), and isoproterenol caused vasodilation. Norepinephrine and epinephrine were of approximately equal potency as vasoconstrictor agents on ia injection. After administration of dibozane, iv, injections of norepinephrine, epinephrine, and isoproterenol all reduced blood pressure, and ia administration of all three agents increased blood flow. Epinephrine and isoproterenol were of approximately equal potency on ia administration as vasodilators after dibozane, but norepinephrine was approximately 1/100 as potent. Propranolol was then given, after which isoproterenol produced small dilator responses, norepinephrine produced small constrictor responses, and epinephrine produced either small constrictor (1 µg/kg, iv; 0.1 µg, ia) or small dilator (1.0 µg, ia) responses. A sample polygraph record is in Figure 1A and a summary of experiments in Figure 2A. Phenoxybenzamine and phentolamine were tested in three experiments each with results similar to those obtained with dibozane. However, the dilation produced by norepinephrine after 30 mg/kg of phentolamine or phenoxybenzamine was not as great as after dibozane.

Perfused Gracilis Muscle Experiments

When given ia before an α-adrenoceptor antagonist, norepinephrine and epinephrine were nearly equipotent vasoconstrictor agents, and isoproterenol was a potent vasodilator in the perfused gracilis muscle. After administration of dibozane, all three amines elicited dilator responses, but norepinephrine was only approximately 1/100 as potent as epinephrine and isoproterenol, which were approximately equipotent. Propranolol then blocked the dilator effects of the three drugs, and large doses of norepinephrine elicited vasoconstriction (Figs. 1B and 2B, gracilis type 1 experiments).

Lumbar sympathetic nerve stimulation elicited vasoconstrictor responses in proportion to stimulus frequency in the perfused gracilis muscle (gracilis type 2 experiment) prior to receptor blockade and vasodilation after. The nerve-mediated vasodilation was cholinergic as shown by the complete blockade...
by atropine and the marked attenuation of acetylcholine-induced vasodilation. The vasodilation evoked by norepinephrine was not antagonized by atropine but was blocked by propranolol, as was that induced by isoproterenol, showing that these responses were \( \beta \) adrenergically mediated. After propranolol, norepinephrine and nerve stimulation again produced vasoconstriction, but because of the continued \( \alpha \)-adrenoreceptor blockade by dibozane, the responses were much smaller than in the control period. The constrictor responses to nerve stimulation after atropine and propranolol were slightly greater than after atropine alone, although this difference was not significant \( (P > 0.05) \). A sample experimental record is shown in Figure 3, and summary data are in Figure 4A.

In those experiments in which the gracilis nerve was stimulated (gracilis type 3), muscle contraction and resultant metabolic vasodilation were blocked by pancuronium. The results (Fig. 4B) were similar to those obtained in type 2 experiments in which the lumbar sympathetic nerves were stimulated; that is, the constrictor effects of nerve stimulation and of norepinephrine were converted to vasodilatation after atropine but was blocked by propranolol, as was that induced by isoproterenol, showing that these responses were \( \beta \) adrenergically mediated. After propranolol, norepinephrine and nerve stimulation again produced vasoconstriction, but because of the continued \( \alpha \)-adrenoreceptor blockade by dibozane, the responses were much smaller than in the control period. The constrictor responses to nerve stimulation after atropine and propranolol were slightly greater than after atropine alone, although this difference was not significant \( (P > 0.05) \). A sample experimental record is shown in Figure 3, and summary data are in Figure 4A.

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3 experiments. Initially, norepinephrine, nerve stimulation, and tyramine produced vasoconstriction. Cocaine blocked the effects of tyramine, prolonged the vasoconstrictor effects of norepinephrine and nerve stimulation, and potentiated the pressor response to the largest dose of norepinephrine (Fig. 4). As in type 2 and 3 experiments, dibozane converted the vasoconstrictor effects of norepinephrine and nerve stimulation to dilation, and atropine blocked the dilation produced by acetylcholine and nerve stimulation but not that produced by norepinephrine. Propranolol then blocked the dilation produced by isoproterenol and reversed the response to norepinephrine from dilation to constriction. The slight augmentation of the nerve stimulation-induced vasoconstriction that occurred in dogs given propranolol after atropine (in type 2 and 3 experiments) was not observed after atropine and propranolol in dogs that had been given cocaine.

In the second series, responses to nerve stimulation, catecholamines, tyramine, and acetylcholine were assessed before and after the administration of propranolol alone (gracilis type 5), and the results compared to comparable experiments using cocaine. In Figure 5, it can be seen that propranolol blocked the dilation produced by isoproterenol, thus demonstrating a high degree of β-adrenoceptor blockade, but did not alter the responses to the other agents. There was no augmentation of the vasoconstrictor effects of nerve stimulation or of norepinephrine.

Cardiac Experiments

Intravenous injections of the three catecholamines produced dose-related increases in heart rate and right ventricular contractile force. Norepinephrine and epinephrine increased diastolic blood pressure, and isoproterenol decreased it. The order of potency of the three agents on heart rate and contractile force based on approximate ED50's was the same: i.e., isoproterenol (0.1 μg/kg) > epinephrine (0.7 μg/kg) > norepinephrine (0.7 μg/kg). Cardiac sympathetic nerve stimulation produced a frequency-related increase in heart rate and contractile force over a range of 0.25–8 Hz, but it had little effect on blood pressure. Administration of propranolol produced a dose-related inhibition of the heart responses to the three catecholamines and to nerve stimulation and blocked the dilator response to isoproterenol. Fifty percent antagonism was achieved with approximately 0.1 mg/kg and 95% with 1 mg/kg (Fig. 6).

Discussion

Our results substantiate the classification of adrenoceptors that subserves vasodilation as β-2 type (Lands et al., 1967; Moran, 1975) and lend support to the concept that these receptors are not innervated, in contrast to α and β-1 adrenoceptors which clearly mediate responses to sympathetic nerve stimulation. Sympathetic nerve stimulation and epinephrine and norepinephrine elicited vasoconstrictor responses before α-adrenergic blockade. Norepinephrine and epinephrine were approximately equipotent, a potency relationship characteristic of α adrenoceptor-mediated responses (Ahlquist, 1948). After α-adrenergic blockade with dibozane, nerve stimulation, epinephrine, and norepinephrine evoked vasodilation. However, neuronaly induced vasodilation, in contrast to that by the catechol-
amines, was entirely cholinergic, i.e., it was completely blocked by atropine. The relative vasodilator potencies of the three catecholamines are characteristic of β-2 adrenoceptor-mediated responses, i.e., isoproterenol and epinephrine were approximately equipotent, and both were much more potent than norepinephrine (Lands et al., 1967; Moran, 1975).

Several investigators have reported dilator responses to sympathetic nerve stimulation (Lundvall and Järhult, 1974, 1976; Tuttle and Moe, 1973; Viveros et al., 1968), whereas others have found none in animals that had received both an α-adrenoceptor antagonist and atropine (Belfrage and Rosell, 1976; Dawes and Faulkner, 1975; Glick et al., 1967; Folkow and Uvnäs, 1950; Rosell and Belfrage, 1975; Youmans et al., 1955; Vatner and McRitchie, 1976).

Viveros et al. (1968) observed vasodilation in the perfused gracilis muscle of the dog in response to sympathetic nerve stimulation after administration of dibozane and atropine, vasodilation that was then blocked by propranolol. Although we used a preparation similar to theirs, there are two differences in experimental design: (1) we compared the potency of three catecholamines to verify the low potency of norepinephrine as a vasodilator, whereas Viveros et al. used only norepinephrine and did not relate the responses to either β-1 or β-2 type of adrenoceptor; (2) we gave dibozane by slow iv infusion instead of by ia infusion as did Viveros et al., because we were able to achieve a high degree of α-adrenoceptor blockade (i.e., the vasoconstrictor effects of norepinephrine, epinephrine, and sympathetic nerve stimulation were reversed), and because slow infusion of the acidic dibozane solution should induce less change in pH of the gracilis muscle when the drug is given by the iv, rather than by the ia route. (Because Dibozane is poorly soluble at neutral pH, it was dissolved in phosphoric acid as described by Rapela and Green, 1961.) Viveros et al. did not indicate how they dissolved dibozane or what effect the diluent alone had on vascular resistance.

Lundvall and Järhult, who studied the effects of sympathetic nerve stimulation on perfusion pressure, segmental resistance, and capillary filtration coefficient (CFC) in cat skeletal muscle reported in one paper (1974) that dibozane converted the vasoconstrictor effect of nerve stimulation to vasodilation in atropine-treated animals. The vasodilation, which was blocked by propranolol, was predominantly confined to the microcirculation.

In a more detailed paper (1976), Lundvall and Järhult administered only propranolol and based their analyses on the assumption that β-adrenergic vasodilation is "located in the micro-vessels, where it significantly can modify the α-constrictor influence." Propranolol did not influence the increase in total peripheral resistance due to sympathetic nerve stimulation, but it augmented the increased microvascular resistance and diminished the increased CFC. Lundvall and Järhult postulated that propranolol blocks β adrenoceptors on precapillary sphincters resulting in unopposed α-mediated vasoconstriction with consequent enhanced microvascular resistance and lessened capillary filtration.

The vasodilation that Lundvall and Järhult reported in response to sympathetic nerve stimulation in atropine-treated cats after administration of dibozane (1974) is similar to that shown by Viveros et al. (1968). They gave dibozane by ia infusion as did Viveros et al. and commented that dibozane, as well as the acidic solvent, decreased resistance initially. The only apparent reason for the difference in our results from those of Lundvall and Järhult and Viveros et al. is that ia administration of dibozane affects the vascular response to sympathetic nerve stimulation in a way that iv administration does not, even though the drug blocks α adrenoceptors by either route.

In addition to the proposed explanation Lundvall and Järhult gave for their results, that is, β-adrenergic blockade shifted the balance between β adrenergically mediated vasodilation and α adrenergically mediated vasoconstriction to a predominant α response, there are two other possibilities. One is an inhibition of vasodilation secondary to a primary blockade of β adrenergically augmented skeletal muscle metabolism. Sympathetic nerve stimulation increases metabolism in the perfused gracilis muscle (Duran and Renkin, 1976) and metabolic factors influence CFC (Mellander and Johansson, 1968). Propranolol, by blocking a β adrenoceptor in skeletal muscle, might have prevented the augmented metabolic effect of sympathetic nerve stimulation and, thus, indirectly inhibited vasodilation and enhanced CFC. A second explanation concerns a prejunctional effect of propranolol. Neither Lundvall and Järhult nor Viveros et al. considered the possibility that the responses they observed were due to inhibition of adrenergic neuronal reuptake of norepinephrine by propranolol (Foo et al., 1968; Eliash and Weinstock, 1971) instead of blockade of β adrenoceptors on blood vessels. Inhibition of reuptake of norepinephrine would result in greater α adrenoceptor-mediated effects due to larger amounts of free norepinephrine at the receptors. Furthermore, if the density of precapillary adrenergic innervation is greater than that of postcapillary innervation in the gracilis muscle, as has been shown for the rabbit mesenteric vascular bed (Su et al., 1977), and if propranolol were inhibiting neuronal reuptake of norepinephrine, the constrictor effects of nerve stimulation on precapillary vessels might be greater than on postcapillary ones, making it appear that the precapillary sphincters were actively dilated to a lesser degree in the presence of, than in the absence of, propranolol.

The slightly augmented vasoconstrictor response to nerve stimulation that we observed after administration of propranolol in dogs that had received...
adjacent to blood vessels would be expected to exert /β-1 receptor is innervated. vated the cardiac adrenoceptor and, thus, that this epinephrine released from adrenergic neurons are not very sensitive to norepinephrine, the nor-

adrenergic nerve terminals and, therefore, should prevent neurogenic adrenergic vasodilation through β adrenoceptors, respectively. Tuttle and Moe (1973) concluded that reflex vasodilation in response to iv administration of epinephrine or veratrine is mediated by β adrenoceptors. However, guanethidine, which they used to eliminate withdrawal of α adrenoceptor-mediated vasoconstrictor tone as a mechanism of reflex dilation, inhibits release of norepinephrine from all adrenergic nerve terminals and, therefore, should prevent neurogenic adrenergic vasodilation through β adrenoceptors as well as constriction through α receptors. Also, cholinergic fibers participate in baroreceptor-mediated dilation (Takeuchi and Manning, 1971, 1973), but Tuttle and Moe did not use atropine and thus could not eliminate a sympathetic cholinergic response. The blocking effect of propranolol on the reflex vasodilation they observed is not readily explained, especially in the presence of guanethidine.

Whereas β-2 adrenoceptors of blood vessels appear not to be innervated, the β-1 receptors of the heart are responsive to sympathetic nerve stimulation (Moran and Perkins, 1958). The order of potency of the three catecholamines on cardiac rate and contractile force that we found (i.e., isoproterenol > epinephrine = norepinephrine) is consistent with a subclassification of the cardiac adrenoceptors as β-1 (Lands et al., 1967; Moran, 1975). The fact that cardiac sympathetic nerve stimulation increases heart rate and contractile force indicates that norepinephrine released from the nerves activated the cardiac adrenoceptor and, thus, that this β-1 receptor is innervated.

Because the β-2 adrenoceptors of blood vessels are not very sensitive to norepinephrine, the nor-

epinephrine released from adrenergic neurons adjacent to blood vessels would be expected to exert little effect. However, the β-2 adrenoceptor is highly sensitive to epinephrine and may function as a hormone receptor, responding to circulating epinephrine released from the adrenal medulla.

Adrenoceptors may have different roles in circulatory adjustments. Rapid adjustments, such as augmented cardiac activity and vasoconstriction in response to postural changes or exercise, are mediated through rapid sympathetic nerve conduction, release of norepinephrine, and activation of cardiac β-1 and vascular α adrenoceptors. Slower adjustments, such as metabolic changes and vaso-
dilation, might be mediated by epinephrine released from the adrenal medulla acting on β-2 adrenergic receptors.

Although one cannot conclude that all β-1 adrenoceptors are innervated and all β-2 adrenoceptors are not, there is greater evidence for innervation of β-1 adrenoceptors than for lack of innervation of β-2 receptors. A number of systems have been claimed to respond to sympathetic nerve stimulation and to have β-1 adrenoceptors. Release of proteins (amylase and tonin or salivary renin) from the salivary glands by sympathetic nerve stimulation (Menzie et al., 1974) has been classified as a β-1 adrenoceptor-mediated effect (Thulin, 1972). Sympathetic nerve stimulation-induced lipolysis (Rosell and Belfrage, 1975; Belfrage and Rosell, 1976), which is blocked by propranolol, has been characterized as a β-1 adrenoceptor-mediated function (Langs et al., 1967; Williams et al., 1976), and adrenergic nerves have been shown by fluorescence histochemistry to terminate on adipocytes (Ballard et al., 1974). Release of renin from the kidney by sympathetic nerve stimulation is blocked by propranolol (Davis and Freeman, 1976), but the β adrenoceptor that mediates this release has been classified both as β-1 (Johnson et al., 1976) and β-2 (Johns and Singer, 1974). The β adrenoceptors that mediate relaxation of tracheal smooth muscle appear to be β-1 based on the relative potencies of norepinephrine, epinephrine, and isoproterenol (Lulich et al., 1976) and to respond to neuronally released norepinephrine (Suzuki et al., 1976). Adrenergic nerves terminate on tracheal smooth muscle cells (O'Donnell and Saar, 1973). Thus, β-1 adrenoceptors in several systems appear to be innervated.

Many tissues that contain β-2 adrenoceptors have an innervation which is harder to isolate and stimulate experimentally than most of the known β-1 receptor-containing organs. Bronchioles of rabbits, sheep, pigs, goats, and bulls are reported to have no adrenergic innervation (Mann, 1971). However, there is no general agreement about sympathetic innervation of the bronchiolar smooth muscle of the cat (Silva and Ross, 1974). Cat bronchioles have been reported to contain β-2 receptors (Lulich et al., 1976). The uterus has also been reported to have β-2 adrenoceptors (Lands et al., 1968). Hamilton and Feigl (1976) provide evidence that coro-
nary blood vessels have β-2 adrenoceptors that receive no functional sympathetic innervation.

In summary, α and β-1 adrenoceptors in the cardiovascular system appear to be innervated by adrenergic nerves and to subserve vasoconstriction and augmentation of cardiac activity (rate, force, and metabolism), whereas β-2 adrenoceptors that subserve vasodilation in skeletal muscle and the heart appear not to be innervated, unless there is a restricted innervation of precapillary vessels as part of microvascular control. In other organs, there is a less definite relationship between innervation and type of β adrenoceptors. Nevertheless, it is tempting to speculate that β-1 adrenoceptors, which are very responsive to norepinephrine, are innervated and mediate responses to sympathetic nerve activity, whereas β-2 adrenoceptors, which are very insensitive to norepinephrine, are functionally non-innervated and serve as hormone receptors for epinephrine from the adrenal medulla.

References

Evidence for lack of innervation of beta-2 adrenoceptors in the blood vessels of the gracilis muscle of the dog.

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