SYMPATHETIC MECHANISMS IN BLOOD VESSELS: NERVE AND MUSCLE RELATIONSHIPS[1,2]

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Viewed from the perspective of 1972, concepts of the adrenergic neuroeffector transmission in blood vessels of a decade or more ago seem rudimentary. Many details of this process have now been elucidated and not only has it been found to be highly complex, but to show a remarkable degree of variation in different parts of the circulation. In this chapter neuroeffector transmission is viewed as a process which in its essentials is common to all parts of the vascular bed; the variations in characteristics found in different vessels are considered as modifications of this common pattern appropriate to the function of particular vessels.

More generalized treatments of the physiology and pharmacology of the peripheral circulation can be found in several recent reviews (1–3) and a book (4). Some specialized aspects are covered in depth by others (5–9) and in the proceedings of symposia (10–12); adrenergic mechanisms and amine transport have been frequently reviewed (13–16).

BLOOD VESSEL STRUCTURE AND FUNCTION

Tissue elements in the vessel wall are arranged in concentric tubes. From within is the *intima*, a lining endothelium, and the *sub-intima*, a distinct layer of connective tissue elements. The *tunica media* contains vascular smooth muscle, usually oriented in a circular or spiral direction and based upon a lattice of fibrous and elastic elements. An internal and external elastic laminae sometimes define its inner and outer limits. A neural *plexus* surrounds and sometimes overlaps with the muscular coat like a sleeve. This plexus consists of interlacing terminal ramifications of postganglionic sympathetic, adrenergic neurons. Axonal envelopes of Schwann cells become deficient near periodic axonal swellings or nodes which are sites of transmitter synthesis, storage, release, and uptake. Encasing the vessel and supporting the invading and emergent nerves, small blood vessels, and lymphatics is the *adventitia*.

[1] Abbreviations used in this chapter: NE: norepinephrine; MAO: monoamine oxidase; COMT: catechol-O-methyltransferase.

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Regulation of vascular muscle tone is effected by changes in the active state of the vascular muscle leading to an alteration in vessel diameter and length, and thus to changes in blood flow, capacity, and wall elasticity. Although vascular muscle cells are often in close apposition, the media is not a functional syncytium. The active state of the individual muscle cells is coordinated by a variety of processes, including the local concentration of vasoactive substances, especially the adrenergic transmitter (*l*–NE), propagated activity between individual cells, and by static and phasic intramural distending forces.

The access of exogenous substances to the tunica media in vivo occurs by diffusion via the intima and adventitia and in some larger vessels from vasa vasoral capillary networks. Movement of substances from the lumen is facilitated, and from the adventitia and neural plexus impeded, by the bulk flow of fluid consequent upon the high intraluminal pressure. Except in perfused specimens, in isolated preparations there is no bulk fluid flow. The majority of data used in this chapter has been accumulated from in vitro experiments. A description of the common in vitro vascular preparations and their advantages, disadvantages and limitations has been recently published (17).

THE MECHANISM FOR ADRENERGIC TRANSMITTER SUPPLY

It is the concentration of neurogenic NE at the α-adrenergic receptors of vascular muscle that determines the influence of the sympathetic innervation on vascular muscle tone. In this section some of the factors that determine this parameter are discussed.

Transmitter Synthesis, Storage, and Release

Studies on the spleen, heart, and vas deferens have led to the proposal that NE lost during sympathetic nerve activation is primarily the newly synthesized rather than the endogenous amine, and that synthesis plays a greater role than mobilization of stored NE in maintenance of transmitter release (18–20). Vascular tissue is certainly capable of synthesizing catecholamines (21–23). In the rabbit aorta, however, endogenous NE was preferentially lost upon sympathetic nerve stimulation; synthesis was enhanced only at an unphysiologically high frequency of stimulation (24). How unique this is to blood vessels will be determined by further study.

Catecholamine content varies extensively among different blood vessels from the same species, ranging from virtually nil to over 3 μg/g wet tissue (25–27). NE content cannot be regarded as a measurement of density of adrenergic innervation, as vessels vary in capacity to take up exogenous NE, and this uptake mechanism most likely helps maintain the storage content (20).

Within the vascular wall, catecholamine-containing nodes identified by the fluorescence histochemical technique correspond to the periodic axonal swellings in the adrenergic nerve plexus seen by light or electronmicroscopic methods. They are the site of NE uptake and storage. Within these nodes, several types of vesicles can be identified. Types 2 and 3 granular vesicles are present in the nodes

of all vessels examined and are presumed to be storage sites for intraneuronal NE. Some vessels also contain the larger granular type 1 vesicle of uncertain functional significance (28). The vesicular localization of NE is supported by the presence of two distinct particulate fractions of H^3-NE in the homogenates of the rabbit pulmonary artery preincubated with H^3-NE. However, an additional extravesicular localization cannot be ruled out, as considerable H^3-NE was also found in the supernatant (24).

The small amounts of endogenous NE released by sympathetic nerve stimulation from isolated blood vessels (29–32) preclude certain detailed analytic studies. Many analytical studies have utilized an alternative simplified procedure in which the vessel catecholamine stores are labeled with H^3-NE (33–35). The fraction of the total NE store released per nerve impulse (fractional release) from isolated vessels as well as the perfused skeletal muscle varies between 10^{-4} to 10^{-5} (27). In all these measurements, phenoxybenzamine was employed with the intention of inhibiting reuptake of released NE or H^3-NE. The recent accumulation of evidence that phenoxybenzamine may increase the release of NE independently of uptake inhibition (36–39) throws some doubt on the validity of these observations. Thus, it remains to be determined whether the fractional transmitter release varies among adrenergically innervated tissues.

Studies of the splenic nerve suggest that the total content of catecholamine storage vesicles, including chromogramin and dopamine-β-oxidase, is released upon stimulation (40). If these vesicles are assumed to be the source of neurogenically released NE in blood vessels, then calculations based upon the NE content, the number of vesicles within a node, and the fractional transmitter release show that one nerve impulse on an average releases less than the NE content of one vesicle per node. One school studying perfused skeletal muscle has inferred that the partial content of one vesicle is released from every node by each pulse (41). Another laboratory suggests that in the pulmonary artery the whole content of a vesicle is released from a node only after a number of pulses (30, 34).

Dimensions of the Adrenergic Plexus

The greater the density of nodes in or near the tunica media, the greater the amount of transmitter that will reach smooth muscle cells and the higher the concentration at the α-receptor. In a recent survey of rabbit vessels a remarkable variation in node density was observed (42).

Quantitative information on the dimensions of the vascular adrenergic plexus is known for only the aorta and ear artery of the rabbit in which the plexus is confined to the adventitio-medial junction (27). The ear artery plexus is 2.6 times thicker than that of the aorta. The numbers of nodes per unit surface area of the adventitio-medial junction of the vessels are in a ratio of 4:1. However, it was found that the net release of transmitter in the ear artery was less than expected from this ratio. It was proposed that this was a consequence of "node crowding": nodes within the confines of the thick plexus function inefficiently

as sites of transmitter release, since they are surrounded on all sides by other nodes which take up the NE they release.

When there is overlap between the nerve plexus and muscle layer, this argument is no longer pertinent, since the transmitter does not have to escape from the plexus to act on the smooth muscle. Such an overlap has been described for a number of muscular arteries of the dog (43), the aorta of the young rabbit (44), and the proximal end of the saphenous artery of the rabbit, a small muscular artery. In the latter, the plexus will often extend two-thirds of the way through the media which *in situ* is about 100μ in thickness (45). Innervation of the carotid artery of the rabbit is restricted to the adventitio-medial junction; on the other hand innervation of the same artery of the sheep overlaps the media (46). Presumably when vessel wall thickness increases beyond a critical level, integration of the medial muscle layer cannot be achieved by transmitter diffusing from a plexus limited to the adventitio-medial junction (see below).

Dimensions of the Neuromuscular Cleft and Diffusion Barriers

In the rabbit pulmonary artery, an elastic artery, the closest neuromuscular distance observed was 0.4μ, the mean "shortest distance" between node and closest muscle was 2μ (47), but an actual diffusion path of 4μ is more likely (30). In the rabbit ear artery the mean closest distance was 0.5μ (48). Neuromuscular separation in rat small mesenteric arteries averaged about 0.5μ and in arterioles ranged from 0.1–0.4μ (49). In the rabbit portal vein the separation is of the order of 0.15μ (50). Although the cleft width becomes narrower the smaller the vessel, only very rarely have separations less than 0.1μ approaching those in the vas deferens or at the skeletal neuromuscular junction been reported.

In elastic vessels there is no anatomical relationship between the axonal nodes and particular muscle cells. Since the distance between nodes and the closest muscle cells is similar to that between two neighboring muscle cells, the transmitter upon release will diffuse radially in all directions in the extracellular space. Thus there will be no anatomical confinement of the transmitter in the region of the node. The relative amount of the l-NE released from the nerve plexus that passes through the adventitia or media depends upon the relative resistance to movement afforded by the tunicae. The apparent diffusion coefficient for NE in the media of the rabbit aorta is 7.3×10^{-7} cm^2/sec (51). The value for the adventitia (4×10^{-6} cm^2/sec, unpublished results), is close to that for free diffusion. The low apparent diffusion coefficient derived for the media is the result of the increased tortuosity of the transmitter path and probably the presence of extracellular diffusion barriers.

The narrower the neuromuscular cleft, the more it becomes a synapse in the usually accepted sense of the word. The area of contact is probably of the order of 1–3μ^2. The characteristics of NE diffusion within the cleft are unknown, but a narrow cleft would tend to restrict the rate of movement of released NE from the immediate environment of the node. Once the transmitter has emerged from the cleft, its density depends upon the relative diffusion coefficients of the two tunicae.

Transmitter Concentration, Distribution, and Movement

The movement of transmitter after release from the adrenergic plexus is considered for convenience in two stages: that within the neuromuscular cleft and that through the remainder of the vessel wall. Features of the immediate spread of NE from its site of release in an elastic artery have been previously presented (30, 34, 52). If the total content of one vesicle is released at one time, then it can be shown that movement of transmitter by radial diffusion can deliver an adequate peak transmitter concentration of 6×10^{-9} M at the closest muscle cell membrane.

Two transmitter concentrations in the region of the adventitio-medial junction can be measured experimentally. Firstly, by matching steady state responses to nerve stimulation with exogenous NE following almost complete blockade by phenoxybenzamine, the mean *peak* concentration at the α-receptors can be approximated (53, 54). Secondly, from the measured intimal catecholamine overflow the concentration of transmitter NE at the adventitio-medial junction necessary to effect such movement through the media can be calculated. For the rabbit pulmonary artery, the values with 10 Hz are 8×10^{-8} M and 5×10^{-8} M respectively (Table 1). In this vessel where there is no effective neuromuscular

TABLE 1. Concentrations of Adrenergic Transmitter Within Adventitio-Medial Junction in Blood Vessels During Sympathetic Nerve Activity[a]

Blood Vessel	At nearest postsynaptic membrane[c]	In intrasynaptic space[d]	In extrasynaptic space[e]
Pulmonary artery (4μ)[b]	6×10^{-9}	8×10^{-8}	$5.\times 10^{-8}$
Ear artery (0.5μ)	6×10^{-6}	3×10^{-7}	3×10^{-8}
Portal vein (0.15μ)	10^{-3}–10^{-4}	2×10^{-5}	2×10^{-9}

[a] Concentrations of NE in molarity. Measurements were made in the presence of phenoxybenzamine.

[b] Mean closest neuromuscular cleft width.

[c] Calculated peak concentration following release of whole content of a vesicle.

[d] Experimentally derived peak concentration at α-receptors within hypothetical or real synapse during maintained nerve activity at 10 Hz.

[e] Experimentally derived mean concentration in the extracellular space within adventitio-medial junction during maintained nerve activity at 10 Hz.

synapse, these values are close to each other, i.e., there is no transmitter concentration gradient between the hypothetical "intrasynaptic space" and the extracellular space at the adventitio-medial junction. These values derived directly from experimental data are confirmed by calculations based solely on the NE content of one vesicle and the neuromuscular distance (30, 34).

The distribution of neurogenic NE in the extracellular space would not be expected to be uniform throughout the thickness of either tunica. From a level similar to those listed above at the adventitio-medial junction, the concentration of NE in the vessel wall should fall off towards both intimal and adventitial surfaces. There is experimental support for this proposition (55). Assuming transmural homogeneity of muscle cell characteristics, this implies a gradient of muscle tone across the vessel wall in a vessel where myogenic propagation of excitation is insignificant. This assumption may not be completely justified. The inner cells of the sheep carotid artery appear to be a little more sensitive to NE than the outer smooth muscle (56). However, the degree of difference does not materially alter the proposition. This uneven transmural distribution of neurogenic NE has prompted the "distribution hypothesis" to explain the relative resistance of neurogenic vasoconstriction to α-adrenergic blockade (57). In contrast, exogenous NE would be expected to effect all muscle cells equally under steady state conditions.

In a vessel with a wide cleft the rate of movement of NE through the vessel wall, and the rate at which the transmitter concentration attains new equilibria would be diffusion controlled and depend on local tissue characteristics.

The influence of the neuromuscular distance on neuroeffector transmission becomes greater the smaller the vessel, when it becomes progressively smaller than the average distance between cells (58). The following transmitter parameters were calculated using a formula derived for the cholinergic synapse (59), assuming a neuromuscular cleft of 0.1μ separation and 1.25μ diameter, a local apparent diffusion coefficient one-third that of free diffusion, and release from a point source at the cleft center. If the total content of one vesicle is released instantaneously within the cleft, or a "synapse" in this case, then the time to peak concentration which is a little less than 10^{-3} M at the center of postsynaptic membrane would be 8μsec and that to peak concentration at the edge of the synapse 1.0msec. If the content of one vesicle was distributed evenly within the cleft, the mean concentration would be 2×10^{-4} M. The time taken for the intra-synaptic concentration of transmitter to fall to 1/1000 of its original value, a concentration still well above threshold of many α-adrenergic receptors, is over 6 sec. In contrast, in the aorta, the transmitter concentration following the release of a single vesicle falls to subthreshold levels within a few msec. To summarize, when the cleft is approximately 0.1μ in width, peak transmitter concentration levels at the nearest muscle cells are achieved extremely rapidly and are some 10,000 times higher than in an elastic vessel. Suprathreshold concentrations are maintained for long periods by the transmitter-confining effect of the narrow cleft. It is of interest that junctional potentials in small mammalian blood vessels of more than 1sec duration have been recorded (60).

A peak postjunctional concentration of 4×10^{-4} M has been derived (31) for the guinea-pig main uterine artery, cleft width 0.2μ. Another vessel that has been studied in some detail in which a narrow cleft (0.15μ) has been established is the portal vein. The peak effective concentration of transmitter at the α-receptors in this vessel is 1.5×10^{-5} M at 10 Hz (53). These receptors are probably confined to sites close to the nerve terminals (61, 62). The concentration in the extracellular space at the adventitio-medial junction is 2.0×10^{-9} M. The contrast with the pulmonary artery, in which these two measurements are essentially equal, is instructive, and implies that in the vessel with a narrow cleft, there is a marked concentration gradient between intra- and extra-synaptic sites during nervous activity. These values also imply that in vessels with a narrow cleft the concentration of neurogenic NE in the muscle layers beyond the cleft is probably below receptor threshold, and thus is functionally unimportant. This argument may not apply to precapillary sphincters, which appear to be ultrasensitive to NE (63).

In Table 1 are included data calculated for the rabbit ear artery with a neuromuscular cleft width of 0.5μ. Experimentally derived peak NE levels during steady state response to nerve activity at 10 Hz are included. In the ear artery, the difference between NE concentration at the α-receptors close to the nerve terminals and that in the extracellular space of the adventitio-medial junction is of the order of 10-fold. Such a transmitter concentration gradient is intermediate between that in the elastic artery and the vessel with a narrower cleft.

As proposed earlier the movement of NE released from the adrenergic plexus can be considered in two stages: that to the subjacent sarcolemma and that through the tunicae adventitia and media. (It will be seen below that there are transmitter disposition and effector response correlates to these two stages.) In the pulmonary artery where there is *no* synapse, movement to the postsynaptic membrane merges with, or is indistinguishable from, that through the tunica media. It is the latter event that is primarily responsible for eliciting an effector response. In the portal vein, it is the NE within the cleft acting on the intrasynaptic sarcolemma that is the functionally dominant component. Vessels with intermediate neuromuscular clefts are expected to exhibit features that reflect a variable combination of the two extremes.

Transmitter Disposition

The adrenergic transmitter, once released, is subject to disposition by enzymatic degradation, diffusional escape, and tissue uptake or binding. The relative contribution of each of these can vary significantly among different vascular neuroeffector systems.

(*a*) *Neuronal uptake.*—The neuronal membrane pump in the rabbit thoracic aorta meets the characteristic criteria of carrier-mediated active transport (64), like that in the rat heart (13). Quantitative differences in the uptake of exogenous NE of as much as two orders of magnitude exist among the rabbit arteries and veins (42). When assessed by labeling the transmitter stores with H^3-NE and

using phenoxybenzamine to prevent transport of NE into the neurone, 80% of the transmitter released from the nerve terminals is normally taken up again (33). Some other arteries are somewhat less (27), and some veins more (65) efficient in this respect but these vessels do not appear to differ fundamentally from other adrenergically innervated tissues.

What distinguishes the neuronal uptake mechanisms in blood vessels is their strategic localization in relation to the effector cells. The neurons in many blood vessels are located on the periphery of the smooth muscle mass, with an immense separation even from the nearest sarcolemma. Thus, the neuroeffector distances range from nearly one to several hundred μ. In contrast to these distances, the effective radius of the neuronal amine pump has been estimated at 0.06–0.08μ (66). Significant neural sequestration of released transmitter after it has acted upon the postsynaptic membrane is unlikely under these circumstances. A similar view has been expressed for exogenous NE (67).

It is our conclusion that neuronal reuptake of released transmitter proceeds independently of the effector cells. It alters the amount of transmitter that reaches the media—that portion of transmitter that reaches the postsynaptic membrane is inactivated mainly by diffusion and enzymatic metabolism (34). Thus, neuronal reuptake does not significantly contribute to the termination of action of transmitter, as thought to occur in other tissues (14–16).

In vessels in which the neuromuscular interval is narrow, the released transmitter may act *in toto* upon the postsynaptic membrane before significant reuptake. The view has been expressed that in this situation the transmitter is inactivated predominantly by reuptake (68) and that the adrenergic receptors may temporarily retain the transmitter to facilitate its reuptake (69). This concept is consistent with the finding that NE concentrations outside the synapse are probably below effective levels (see above). Implicit in these views is the conclusion that the inactivation of transmitter by neuronal uptake simultaneously terminates its action.

Thus, the magnitude of the neuromuscular interval must be deemed an important factor in determining the role of neuronal uptake in the transmission process. This is also borne out by the inverse relationship that exists between the synapse interval and the sensitizing effect of cocaine in various adrenergic neuroeffector systems (28), and the failure of rabbit aortic strips to become hypersensitive to NE after acute surgical denervation (67, 69a).

(*b*) *Extraneuronal uptake.*—The uptake of NE by nonneuronal structures in vascular muscle from several sources has been shown using the fluorescence technique (70), and in the media of the rabbit aorta and noninnervated human umbilical artery by conventional isotopic procedures (71, 72) and by a frozen-section technique (73). This uptake occurs at NE concentrations far lower than originally thought. Intracellular catabolism of NE has previously prevented its detection (74).

The extracellular or intramuscular retention of NE may buffer its diffusional loss, and prolong its effect (75), perhaps through its subsequent redistribution

from some muscular compartments to the receptors in the biophase (76). If adrenergic receptors reside within cell membrane or, at any rate, beyond a diffusion barrier in vascular smooth muscle (77, 78), the muscle uptake process may be responsible for the access of NE to these receptors. Above all, muscle uptake coupled with enzymatic degradation represents the major pathway of inactivation of NE present within the vessel wall, particularly in sparsely innervated structures (34, 74). The potentiation of vasoconstrictor responses to catecholamines and increase of transmitter output following sympathetic nerve stimulation by some steroids may be attributed to an inhibition of extraneuronal uptake (32, 79).

(*c*) *MAO and COMT.*—Using the rabbit pulmonary artery with its transmitter stores labeled with H^3-NE, nearly 50% of the total tritium that overflowed during sympathetic nerve stimulation represented metabolic products of NE. Of these, the deaminated catechols constituted a small fraction, the remainder being O-methylated metabolites (33). This is in keeping with the enhancement of aortic and pulmonary artery responses to sympathetic nerve stimulation by inhibitors of COMT but not MAO (80, 81). For exogenously applied NE, disposition by COMT also seems to predominate over that by MAO or neuronal uptake in the rabbit aorta (82). On the other hand, the response of dog saphenous vein to sympathetic nerve stimulation was potentiated by inhibition of either MAO or COMT (83), and MAO was found to supersede COMT or neuronal uptake in the inactivation of exogenous NE (84). Norepinephrine released by sympathetic nerve stimulation in skin and muscle blood vessels was increased by an inhibitor of MAO (85), and that in the portal vein increased by inhibitors of MAO and COMT used in combination (32). Although quantitative comparisons of these results are precluded by the diversity in experimental conditions, they indicate significant enzymatic inactivation of neurogenic or exogenous NE.

When a segment of the rabbit aortic wall was cut into slices of 25μ thickness parallel to the intimal surface and the slices individually assayed, both MAO and COMT activities were found in the medial slices. The activities dropped abruptly at the adventitio-medial junction, the site of the nerve terminals, and were negligible in the outer adventitia (86). By a histochemical method, MAO in the rabbit central ear artery was also found in the media and not at the adventitio-medial junction (87). Furthermore, the MAO and COMT activities in the rat blood vessels were unaffected by immunosympathectomy (88) or 6-hydroxydopamine (89). The MAO and COMT activities of a number of rabbit arteries and veins varied in parallel, quite independently of the density of adrenergic innervation (42). These findings support the extraneuronal preponderance of the two enzymes.

The above argument, however, should not be taken to discredit the role of neuronal catabolic enzymes. Neuronal MAO has been shown to be functionally more important than the extraneuronal MAO in the rabbit ear artery (90). In the cat nictitating membrane, MAO has been found predominantly within the nerve endings (91). Neuronal and extraneuronal MAO may differ in many

characteristics, as this enzyme occurs in multiple forms (92). There is as yet no evidence for neuronal COMT in blood vessels. In any event, extraneuronal COMT and to a lesser extent, MAO, are evidently of considerable functional significance especially in vessels in which adrenergic innervation is sparse and neuromuscular separation wide, and neuronal uptake and extraneuronal metabolism occur independently of each other (93, 94).

(*d*) *Diffusional loss.*—Sensitive assay methods have demonstrated measurable plasma levels of NE in man at rest (95). As this NE originates mainly from adrenergic nerves in the vascular tree (23), it follows that some released NE escapes from the effector organ unmetabolized.

Using H^3-NE as a tracer in the isolated superfused rabbit pulmonary artery, approximately 30% of tritium activity recovered in the bathing fluid in the absence of neural activity represented intact H^3-NE. This rose to over 50% during sympathetic nerve stimulation (33). The amount of tritiated material that traversed the adventitia was several-fold greater than that which crossed the media. Thus, a considerable portion of the transmitter that leaves the plexus may be lost via the adventitia (34). The conclusion that in large vessels, along with uptake and metabolism, diffusion of transmitter through the interstitial spaces plays a significant role in its inactivation cannot be avoided.

Unmetabolized transmitter is also recovered from limb perfusates following sympathetic nerve stimulation (68, 85). This transmitter must originate in the main from small vessels. It is not known whether downstream concentrations of transmitter are effective. Our calculations suggest that extrasynaptic concentrations are low (see above), yet some small vessels are extremely sensitive to NE (63).

THE TUNICA MEDIA AS AN EFFECTOR ORGAN

Organization of the Medial Smooth Muscle

In general, the medial muscle cells are arranged in a low-pitch helix (96) and in larger vessels organized into bundles (97, 98). Presumably as in other smooth muscle tissues, these bundles frequently subdivide and anastomose with each other. These bundles may constitute functional units. If a critical cross-sectional mass is necessary to support regenerative propagation (a diameter of 100μ has been proposed for some nonvascular muscle; 7, 99, 100), then subdivision of bundles in the wall of the blood vessel might tend to restrict the extent of the functional unit. Nexi or tight junctions between cells where the outer lamella of the plasma membrane fuse have been described in both large and small vessels. More common are areas of close contact between cells (8). End-to-end and side-to-side associations have both been seen. A survey of the literature gives the distinct impression that intercellular contacts become more frequent as vessels become smaller (5, 101). It is noteworthy that at least down to the small arteries, the smaller the vessel the greater the distance of propagation of local excitation (102).

Considerable quantitative differences in response to NE exist in different parts of the vascular tree and even between adjacent segments of a given vessel (45, 63, 103, 104). The basis of this variation and, in most instances, its significance is unknown.

Coordinating Mechanisms in the Media

The placement of the neural plexus in a discrete plane within the vascular wall raises the problem as to how the transmitter can regulate the tone of muscle coats many layers thick. The predicted characteristics of possible mechanisms of coordination are described below.

(*a*) *Diffusion.*—Transmitter diffusion furnishes a slow mechanism of coordination. For example, the time taken for NE entering from one surface to "saturate" the medial extracellular space of the rabbit ear artery and aorta is approximately 1.5 and 10 mins, respectively (105). Whenever muscle coordination is dependent upon such diffusion, a transmural gradient of effect would be inevitable (see above).

In a vessel in which medial contraction is dominated by diffusion, NE will probably initiate a tonic contraction in the absence of change in membrane potential or in association with slow graded membrane potential change (106–109). The coupling under these circumstances has been termed pharmacomechanical coupling. Since there are many examples of a dissociation between these two events, there is some question concerning the significance of the membrane potential change when it occurs.

(*b*) *Electrotonic spread.*—Vascular smooth muscle exhibits cable properties (110).Thus an electrotonic potential spreads with an exponential decay along the vessel wall. The space constant for the rabbit common carotid artery is 1.1 mm (111). In the rabbit ear artery with a muscle wall thickness of about 100μ, assuming the space constant in the radial axis to be 1 mm, a potential change elicited in cells at the outer media would only fall by about 10% at the inner cells. In the longitudinal axis, assuming the same space constant, its range of influence would perhaps be limited to only several mm.

(*c*) *Slow potential activity.*—Various blood vessels have been reported by many authors to exhibit rhythmic contractile activity of slow frequency (7, 112). This type of contraction has been observed in some 30 different vessels from the rabbit (42). In the vessel exhibiting slow rhythmic contractions, adjacent areas generated slow, fairly sychronous changes in membrane potential (113). That propagation of excitation can occur via this mechanism is suggested by studies on intestinal muscle (114).

We propose that the potentiality for slow rhythmic activity is present in most vascular tissues under in vitro conditions. Since slow, low-amplitude oscillations in membrane potential can be observed in vessel preparations while they appear as a whole to be mechanically quiescent, it may be that such activity is usually

synchronous only within a bundle, the functional unit of the vessel, activity in different bundles being out of phase with each other. Drug addition, sudden stretch, or some other stimulus that acts simultaneously on the whole tissue serves to synchronize the slow wave activity throughout the tissue. This would show itself as a slow oscillation in tension. For example, a depolarizing drug would act simultaneously on all cells subjacent to the entire tissue surface and as a result of electrotonic spread, influence all muscle units within the tissue. The effect of this would be to "phase-lock" the previously independent slow potential activity. The synchronized membrane potential changes throughout the tissue would be linked with generalized rhythmic contraction waves.

(*d*) *Regenerative or action potentials.*—Smooth muscle action potentials have been recorded in a number of vascular tissues (7, 9). In the longitudinal muscle of the portal vein and anatomically associated mesenteric veins of several species, there is little doubt that action potentials reflect myogenic propagation of excitation (114a). The longitudinal muscle in the rat portal vein is approximately 70μ in thickness and arranged in clearly defined bundles (115).

In the smaller muscular arteries, veins, and arterioles, it seems likely that the thickness of the muscle wall is inadequate to sustain regenerative propagation. In the larger conduit vessels, on the other hand, elastic laminae break up the media into thin contiguous sheets of only one or two cells thick. Spontaneous action potentials recorded from various small vessels of the frog and from mesenteric arterial muscle cells had the shape of pacemaker potentials, i.e. were nonpropagated, and were graded (9). They may be equivalent to the abortive action potentials initiated by intracellular electrodes in smooth muscle syncytia which remain fairly localized (116).

The evidence available suggests that coordination of the vessel wall by means of propagated action potentials is comparatively rare in the vascular tree. Abortive, locally propagated activity may be more common. When NE acts by propagated action potentials, it may do so by increasing the activity of existing pacemaker cells, by initiating new pacemaker activity and by influencing conduction properties of a tissue.

Not all would agree that medial coordination is achieved by only postsynaptic mechanisms. Evidence suggests that the longitudinally propagated vasodilatation in the microcirculation may be mediated by neural pathways (117). Although this concurs with a number of earlier findings, the role of this mechanism is not certain.

SYNTHESIS AND SUMMARY

Almost without exception blood vessel walls have a number of common features: (*a*) an adrenergic plexus, the site of transmitter synthesis, storage, release, and reuptake, separated to a varying extent from (*b*) an effector organ made up of layers of smooth muscle cells, which possess the potentiality for intrinsic rhythmic activity and contain transmitter degrading mechanisms.

Within this framework, blood vessels exhibit remarkable differences. Many

of the differences can be related to variation in these common features, specifically the plexus thickness, the width of the neuromuscular cleft, the thickness of the muscle wall, and the frequency of muscle cell contact. Other differences between vessels relate to special local features, such as the presence of longitudinal muscle, inherent myogenic basal tone, nonadrenergic transmitter mechanisms, and unusual receptor populations.

Some of the consequences of variation in these common features will be explored and in the same context, the neuroeffector machineries in several different types of vessels characterized.

Plexus density and thickness.—These show variation even in different parts of the same vessel. The greater the plexus thickness and density the greater the potentiality for neurogenic muscular tone, although net transmitter release does not increase proportionately with these parameters because of the node-crowding effect.

Cleft width.—Where the neuromuscular distance is large, a functional synapse is nonexistent: The transmitter enters the muscle layer as from a circumferential "sprinkler system", and there is no confinement of the transmitter to the cleft. Transmitter is taken up by the adrenergic neurones largely before it enters the media; thus primarily extraneuronal mechanisms are responsible for termination of the transmitter action.

With decreasing cleft width, the transmitter tends to be more confined within the synapse. Intrasynaptic transmitter concentration, the intra- to extra-synaptic concentration difference, and the proportion of transmitter neuronally sequestered after its action on the post-synaptic membrane all increase. The extraneuronal mechanisms become less important in the termination of transmitter action. The higher the intra-synaptic NE concentration, the greater the likelihood of initiation of action potentials.

Media thickness.—This varies independently of either plexus density or cleft width. A minimum thickness of media is necessary to support propagated electrical activity. The thicker the muscle mass the longer the time taken for the diffusion-limited response to reach a steady state, the smaller the neurogenic response in comparison to maximum response to exogenous NE, the greater the proportion of transmitter inactivated extraneuronally, and the smaller the proportion of unmetabolized NE in the intimal overflow.

Frequency of muscle-muscle association.—This parameter is reflected in the cable properties of the vessel. Since the cable properties of the rabbit common carotid artery and the rat portal vein are similar (110, 111), frequency of contact and myogenic propagative activity do not parallel each other. Contacts are a prerequisite for propagation. However, the mechanism and importance of propagation in a particular vessel depends upon other cellular and membrane characteristics. These have not been defined.

These generalities will be illustrated with specific reference to four vessels.

Rabbit pulmonary artery.—(Neuromuscular cleft width 2μ; media thickness 250μ). The plexus is of low to medium density occurring in one plane. A large proportion of the released transmitter is neuronally taken up mostly before it reaches the media. The contractile response to NE is predominantly diffusion-controlled and associated with either no change in the membrane potential or a slow graded depolarization. The maximal response to nerve stimulation is much smaller than that to exogenous NE. Most of the transmitter that enters the media is bound or metabolized extraneuronally before it emerges from the intima.

Rabbit ear artery.—(Neuromuscular cleft width 0.5μ; media thickness 100μ). This artery exhibits a biphasic response to neurogenic or exogenous NE. These phases are dependent upon two coupling modes in the media (118–120). The plexus is dense and thick. High intrasynaptic concentrations of transmitter are attained, and are responsible for an early myogenic, propagated response. Sufficient transmitter enters the media to elicit the second phase of response which is diffusion-controlled. The ratio of responses to neurogenic and exogenous NE is high. Both neuronal and extraneuronal mechanisms are responsible for terminating the action of the transmitter.

Rat portal vein (*longitudinal muscle layer*).—(Neuromuscular cleft width 0.15μ; media thickness 70μ). Plexus density is lower than in the pulmonary artery. Extremely high intra-synaptic transmitter concentrations are achieved. The majority of the α-adrenergic receptors are located close to the nerve terminals (61). Coordination is the result of myogenic propagation of action potentials. Supposedly termination of transmitter effect is primarily by neuronal re-uptake. The amount of NE that overflows from the cleft realizes only low concentrations in the media. Responses to neurogenic and exogenous NE are almost equal in magnitude.

A mathematic model of the neuroeffector system of the portal vein has been formulated (61). A single receptor-agonist reaction determines the α-adrenergic response to neurogenic and exogenous NE, presumably because of the limited locale of the receptor.

Speculation concerning small arteries and large arterioles.—(Neuromuscular cleft width 0.1–0.2μ; media thickness $< 50\mu$). Plexus density is highly variable, leading to variability in responsiveness to nervous activity. Supposedly high intra-synaptic transmitter concentrations are achieved and ineffective amounts of NE overflow from the synapse. Local consequences of extraneuronal uptake and metabolism are minimal. Neurogenic effects are terminated mainly by neuronal reuptake of transmitter. Coordination is by local myogenic processes; presumably such coupling is related to the frequency of contacts between muscle cells.

The implication of these descriptions is that given a comparatively few data of primarily morphological nature, it may be possible to deduce the characteristics of the neurogenic response of even diverse vessels. Experimental confirm-

ation of this facility in a number of instances would substantiate the predictive value of this approach. With additional information, a more complete description of blood vessels in terms of a small number of common, but variant components may be possible. In tissues that have so much in common yet appear to show great differentiation, this goal may not be unrealistic; in fact it may provide a needed direction of effort.

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