Do Precapillary Sphincters Respond to Vasoactive Substances in an All-or-None Manner?[1] (35877)

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Evidence has accrued to indicate that whatever mechanism or mechanisms may be responsible for local control of blood flow in the peripheral circulation, the overall function of local regulation of blood flow is to insure tissue homeostasis via an establishment of optimum transcapillary exchange function (1–6). That is, these local factors must interact synergistically with systemic factors to promote optimal nutritional blood flow to the various regional tissues. This must be achieved by a fine regulation and distribution of blood flow into, as well as out of the true capillaries. Vasomotion or the cyclical opening and closing of metarterioles (or thoroughfare channels) and precapillary sphincters is thought to be the major mechanism, in the microcirculation, by which blood flow is ultimately regulated into the true endothelial capillary exchange vessels (2–4). To a large extent, the precapillary sphincters are thought to determine the distribution of blood to the capillaries as well as dicate the surface area available for transcapillary exchange (2–8).

It is generally assumed, *in vivo*, that the precapillary sphincters composed of one or two smooth muscle cells, originating at the junction of many true capillaries and metarterioles (9–11), respond myogenically to changes in blood pressure as well as to various nervous, humoral, and metabolic factors in an all-or-none manner (2, 4, 8, 12). That is to say, these precapillary sphincters are currently thought by most investigators to completely close or open in response to intrinsic and extrinsic stimuli. Moreover, these microcirculatory components are thought to be incapable of responding in a graded fashion to any intrinsic or extrinsic stimulus (2, 4, 8, 12). Up until now, however, this purported fundamental all-or-none property of precapillary sphincters has not received adequate quantitative, investigative attention. Recently, an image-splitting television microscope recording system has been developed which allows one to rapidly make, *in vivo*, accurate quantitative measurements up to magnifications $\times 6500$ on a television screen of the different components of the mammalian capillary bed (13, 14). (The use of this image-splitting device allows one to make measurements with an accuracy 10 times that of the resolving power of the light microscope (15).

The present report, employing this quantitative technique of Baez (13), unequivocally demonstrates that precapillary sphincters not only contract in a graded dose-dependent manner to catecholamines but respond to extremely low (physiologic?) doses of these substances.

Methods. The experiments were carried out *in vivo* by direct microscopic observation of precapillary sphincters in mesentery of the anesthetized rat. The rat mesentery was prepared and kept under physiologic conditions according to procedures described previously (16). Measurements for changes in precapillary sphincter lumen size were made before (control) and after topical application of graded doses (six to eight in number) of the catecholamines epinephrine (Adrenaline hydrochloride, Parke, Davis and Co.), norepinephrine (noradrenaline bitartrate, Le-

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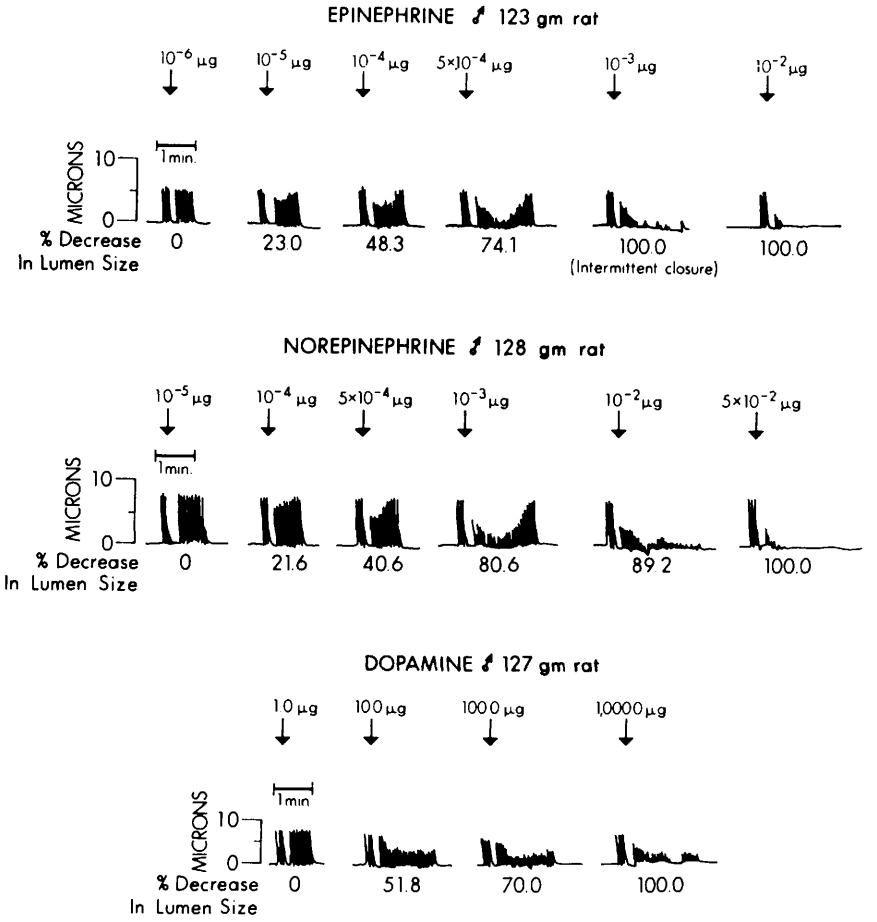

FIG. 1. Electographic recordings of the effects of topically applied graded doses of catecholamines on lumen sizes of precapillary sphincters in rat mesocecum: Each electrographic deflection is a value of the vessel lumen diameter (μ) at the instant of measurement. The space in the electrogram (immediately after arrows) represents the time necessary for the observer to initiate image-splitting following local application of the catecholamines. The doses also refer to the salts in Fig. 2.

vophed, Winthrop Labs) and dopamine hydrochloride (Sigma Chemical Co.). *In vivo* microscopic observations for discrete drug effects were made at magnifications up to approximately 4000 times using the image-splitting television microscope recording system (13). Leitz-Ultrapak water immersion objectives, 55× and 75×, were used in conjunction with 10× Bausch and Lomb oculars on a Bausch and Lomb Dyna-Zoom microscope equipped with a trinocular head.

Results and Discussion. Figure 1 shows the electrographic recordings of typical changes in precapillary sphincter lumen sizes, seen in three different rats, in response to graded constrictor doses of the catecholamines. Topical application (0.1-ml volumes) of all three catecholamines, in increasing doses, resulted in dose-dependent contractile responses which were clearly not an all-or-none phenomenon. Figure 2 shows the relative sensitivity of the precapillary sphincters to the three naturally occurring catecholamines and thus indicates that these vessels are quantitatively more sensitive to epinephrine and norepinephrine than heretofore believed, responding to threshold doses of 10^{-5} to 10^{-4} μg/ml. (These vessels are even more sensitive to these catecholamines when they are locally administered intra-arterially through a branch of

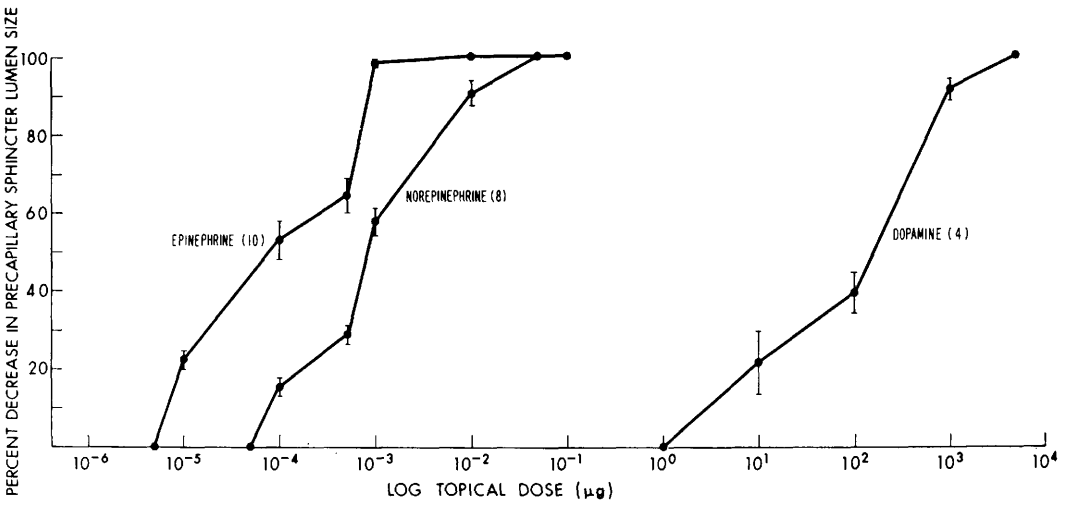

FIG. 2. Graded contractile responses of precapillary sphincters to topically applied catecholamines: Each point represents the mean value obtained from measurements on vessels from different male rats (indicated by numbers in parentheses). Only one type of catecholamine was tested on each rat mesentery. The bars represent the SEM. The mean control lumen sizes for the precapillary sphincters were: ($\mu \pm$ SEM): epinephrine, 6.4 $\pm$ 0.3; norepinephrine, 7.4 $\pm$ 0.6; and dopamine (5.6 $\pm$ 0.4).

the ileocolic artery (17)). Other quantitative data indicates that these vessels are on the average 500–1000 times more sensitive to the constrictor actions of epinephrine and norepinephrine than are the arterioles (17). Rat plasma epinephrine and norepinephrine levels measured recently by Chin and Evonuk (18) are on the average between 6–8 $\times$ 10^{-3} μg/ml. In other words, these precapillary sphincters respond to circulating plasma catecholamine levels.

It is also interesting to note that although these precapillary sphincters can also contract to closure in a graded fashion to dopamine (Figs. 1 and 2), they are relatively insensitive to this catecholamine. Dopamine was not, however, found to be capable of eliciting vasodilatation on any of the precapillary sphincters that were examined. This finding is of interest in relation to several recent reports in which dopamine, by gross resistance and flow measurements, has been found to be a vasodilator in the splanchnic area in dogs (19, 20).

The present data unequivocally demonstrate that precapillary sphincters respond to different catecholamines in a dose-dependent graded fashion, at least for rat mesentery. Preliminary results (to be published elsewhere) show that other constrictor substances such as the polypeptides, vasopressin, and angiotensin, as well as dilators like histamine and bradykinin, also are capable of inducing graded responses in rat mesenteric precapillary sphincters. Furthermore, we have not observed all-or-none type responses with any of these vasoactive substances. Such data strongly suggests that precapillary sphincters, where they exist, are able to *very finely regulate* transcapillary exchange by more actively changing capillary pressure and blood flow than is currently believed.

Summary. Precapillary sphincters are currently thought by most investigators to completely close or open in response to intrinsic and extrinsic stimuli. *In vivo* experiments, using the rat mesentery and a high magnification (up to $\times$6500) image-splitting television microscope recording system, were designed to test this hypothesis. The results clearly, and quantitatively, demonstrate that precapillary sphincters, at least in rat mesentery, do not respond (*i.e.*, constrict or dilate) to vasoactive substances in an all-or-none

manner but in a dose-dependent, graded fashion.

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