Sensitivity of Mesenteric Vascular Bed to Vasoconstrictor Drugs During Reactive Hyperemia

DETAR and BOHR[1] have found that the contractile response to norepinephrine of helical strips of rabbit aorta is a function of pO_2 in bathing solution. As GUYTON et al.[2] have found that the most potent factor in reactive hyperemia is the exhaustion of oxygen in the vascular muscle, we investigated whether a depression of sensitivity to norepinephrine and angiotensin of canine mesenteric vascular bed occurs during the reactive hyperemia. Such depression was found in the present study.

Method. The mesenteric vascular bed in 11 mongrel dogs anesthetized by α-chloralose (100 mg/kg i.v.) was perfused in situ with arterial blood using a constant flow perfusion system[3]. To evoke reactive hyperemia in the perfused vascular bed lasting several min, it was necessary to interrupt the blood flow in this region for 90 sec at least. Hence, the duration of arterial occlusion was 2.58 ± 0.08 min ($\bar{x}$ ± S. E.). Angiotensin (Hypertensin® Ciba) or norepinephrine (Noradrenalin® Spofa) were administered in doses equal to ED_{40} (0.1–1.0 μg) into superior mesenteric artery in the control period, during and after the reactive hypermia. Consequent changes in perfusion pressure were measured (Figure 1).

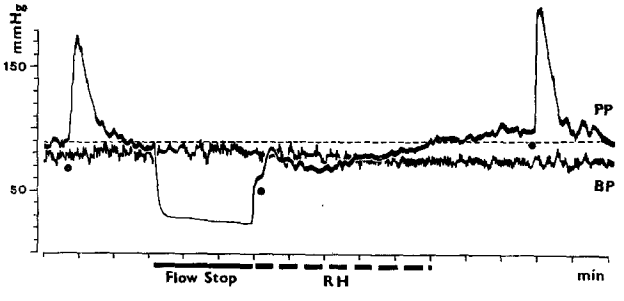

Fig. 1. Vasoconstrictor responses of canine mesenteric vascular bed to angiotensin (0.1 μg i.a. at ●) in the control period and during and after the reactive hyperemia (RH) induced by arterial occlusion (flow stop). PP and BP mean perfusion and systemic arterial blood pressures, respectively. Note the decrease in the pressor response during the reactive hyperemia.

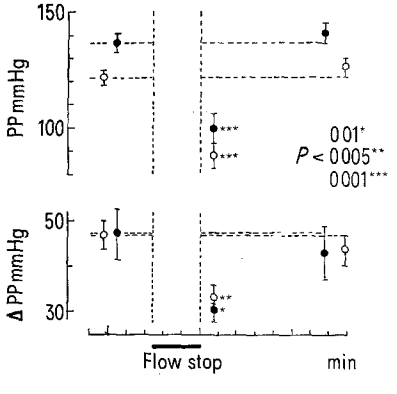

Fig. 2. Initial perfusion pressure (PP) in canine mesenteric vascular bed and change in the perfusion pressure (△ PP) after the administration of single doses (ED_{40}) of angiotensin (○) or norepinephrine (●) in the control period and during and after the reactive hyperemia. Each point ($\bar{X}$ ± S.E.) in angiotensin and norepinephrine groups was calculated from 44 measurings in 11 animals and 35 measurings in 9 animals, respectively.

Results. Summarized data of all experiments are shown in Figure 2. The decrease in the perfusion pressure indicating the reactive hypermia, measured 0.73 ± 0.06 min following the occlusion period was highly significant. This vasodilatation was not present 6.6 ± 0.4 min later. Concurrently, changes in the sensitivity of perfused vascular bed to angiotensin and norepinephrine occurred. The pressor responses to these drugs were significantly diminished during the reactive hyperemia. The responses measured 7 min later did not differ significantly from those measured in the control period.

The pressor responses to both drugs measured in the control period, and during the reactive hyperemia plotted against the respective values of the initial perfusion pressure, are shown in Figure 3. There is significant correlation in both plotes ($r = 0.292$ and $r = 0.281$), while slopes of both regression lines are not significantly different ($b = 0.196$ and $b = 0.193$ in angiotensin and norepinephrine group, respectively). Consequently, the depression of vasoconstrictor sensitivity to both drugs is related to the vasodilatation induced by arterial occlusion in very similar way.

Discussion. SELKURT et al.[4] demonstrated that the reactive hyperemia in the canine ileum is metabolic in origin. Correspondingly, GUYTON et al.[2] stated that the most probable cause of reactive hyperemia is an oxygen deficiency per se in the vascular muscle. Oxygen saturation in blood and tissue was not measured in our experiments. However, using data published by SELKURT et al.[4], an approximation of oxygen saturation during the reactive hyperemia can be done[5]. According to that, a considerable tissue hypoxia was apparently present at the moment when the decreased responses of perfused vascular bed to both drugs were measured.

SHIBATA and BRIGGS[6] described a depression of contractile responses to various vasoconstrictor stimuli of isolated strips of rabbit aorta during anoxia. DETAR and BOHR[1] using the same preparation have found a close dependence of the contractile tension and the contractile response to epinephrine on pO_2. They presumed a rapidly reversible metabolic mechanism depending on pO_2 which controls the production of high energy intermediates necessary for vascular muscle contraction, and assumed it might have a role in local autoregulation of blood flow. Our observation could be fully explained on the basis of this hypothesis. However, other factors such as changes in pH[7,8] and/or changes in wall/lumen ratio of blood vessels[9] occurring during the reactive hyperemia might also contribute to the observed phenomenon.

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[5] The canine intestine goes into an oxygen debt approximately in 1 min of complete ischemia[4]. In our experiments ischemia lasted 2.56 ± 0.08 min, hence the oxygen debt apparently occured. Using data for tissue blood volumes and oxygen consumption found by SELKURT et al.[4] the oxygen debt can be calculated. It was approximately 1.2 ml O_2/100 g of tissue at the end of the occlusion period and was repayed approximately 1.1 min after restarting of perfusion.
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Contrary to our observations, ABRAMS et al.[10] have found an increased sensitivity to intra-arterially administered epinephrine and norepinephrine in human forearm following an arterial occlusion. This vascular bed, however, is complicated by parallel coupling of muscular and cutaneous circulations. A redistribution of blood flow from one region to another could be responsible for this finding[11].

The remarkable similarity of the results obtained with both drugs used in our experiments indicates that the mechanism responsible for the depression of pressor respones during the reactive hyperemia is probably nonspecific in nature. If the decrease in sensitivity of vascular bed to vasoconstrictor stimuli during the local hypoxia is a general phenomenon, it can be an important regulating mechanism helping to improve the local oxygen supply of tissues by diminishing the effect of any vasoconstrictor substance coincidentally present in the arterial wall.

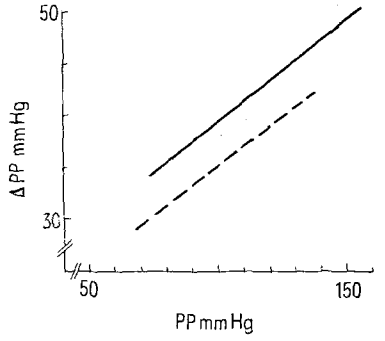

Fig. 3. The relationship between vasoconstrictor responses of canine mesenteric vascular bed (△ PP) to single doses (ED_{40}) of angiotensin (full line) or norepinephrine (broken line) and initial perfusion pressure (PP). Changes in the initial perfusion pressure were induced by preceeding arterial occlusion.

Zusammenfassung. Nachweis, dass die Reaktion der mesenterialen Blutgefässe beim Hund nach einmaliger intraarterieller Injektion von Angiotensin oder Noradrenalin während der durch die 2,5 min andauernden arteriellen Oklusion ausgelösten reaktiven Hyperämie herabgesetzt wird. Diese Verminderung der vasokonstriktorischen Reaktion dürfte insbesondere auf eine Sensibilitätsverminderung der Gefässmuskeln auf die Pharmaka und dessen bei der reaktiven Hyperämie verminderten pO_2 in Blut und Gewebe zurückzuführen sein.

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Cytochemical Localization of 5-Hydroxydopamine in Adrenergic Elements of Cat Adrenal Medulla

A number of experiments by different researchers have demonstrated atypical nerve fibres in the adrenal medulla that do not conform to the widely held principle of preganglionic cholinergic innervation[1–3]. Denervation of the adrenal gland results in the persistent presence of nerve fibres that do not degenerate, even after sectioning of the splanchnic nerve as proximally as the coeliac ganglion[1] or after sectioning the thoracic and first two lumbar spinal nerves[2]. Light microscopy clearly demonstrates bipolar or multipolar nerve cells in the adrenal medulla[3,4] while adjunct cholinesterase reactions reveal additional fibres that either are cholinesterase negative[5] or demonstrate pseudocholinesterase activity following denervation[3]. In addition with electron microscopy postganglionic nerve ending morphology has been described formerly in dogfish[6] and in toad adrenal medulla[7].

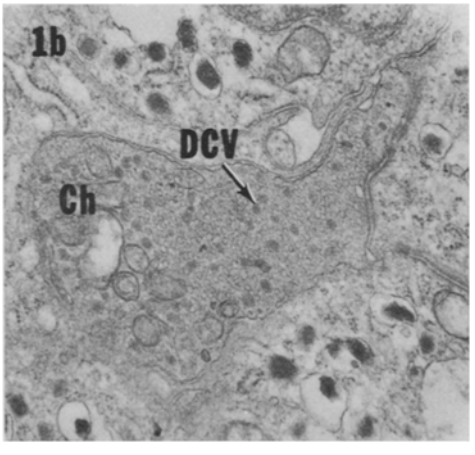

Fig. 1. b) Cholinergic (Ch) nerve ending of control cat adrenal medulla. A typical synapse at the chromaffin cell surface is seen; there are dense cored (DCV) and hollow vesicles neither demonstrating positive reaction for NE or 5-OHDA. ×20,332.

The question of whether or not adrenergic nerves are present in the adrenal medulla still remains due to the lack of a technique that distinguishes histochemically adrenergic from the greater number of cholinergic nerve fibres and endings. 5-Hydroxydopamine (5-OHDA) provides a precise labelling of adrenergic nerves as determined in earlier experiments examining other organ structures[8,9].

5-Hydroxydopamine has been shown to be selectively taken up by adrenergic nerve fibres and accumulated in nerve ending vesicles. Qualitative procedures done in this laboratory have demonstrated a definite reaction of precipitate formation between 5-OHDA and combination

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