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The effect of long-term administration of α_1-blocker prazosin on capillary density in cardiac and skeletal muscle

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Abstract. The effect of prazosin on heart and muscle blood flow and capillary density was studied in rats. In acute experiments, α_1-blocker prazosin almost trebled blood flow in fast skeletal muscles [tibialis anterior (TA) and extensor digitorum longus (EDL)], but did not affect coronary flow when infused i.v. at a dose of 0.5 $\mu g \cdot ml^{-1} \cdot min^{-1}$ for 30 min. Prazosin in an equivalent dose was then given orally over a period of 5 weeks to investigate its effect on capillarisation in heart and skeletal muscle. Capillary density (CD, capillaries $\cdot$ mm^{-2}), estimated in frozen sections stained for alkaline phosphatase, was similar in the hearts of prazosin-treated and control rats. Capillary/fibre ratio in skeletal muscles increased from 1.52 ± 0.019 in control EDL to 1.69 ± 0.01 ($P < 0.001$) and from 1.56 ± 0.04 in control TA to 2.16 ± 0.04 ($P < 0.001$). In TA, the increase was greater than in EDL both in the glycolytic periphery (from 1.30 ± 0.13 to 1.75 ± 0.11, $P < 0.025$) and the oxidative core of the muscle (from 1.837 ± 0.14 to 2.51 ± 0.12, $P < 0.005$). Unilateral crush of the lateral peroneal nerve and subsequent reinnervation over the next 7 weeks resulted in redistribution of fibre types from a typical mosaic pattern into groups composed of fibres of similar oxidative capacity. Capillary density as well as capillary/fibre ratio in purely glycolytic areas was lower when compared to supply of glycolytic fibres in normal muscles. Oral administration of prazosin over the whole period of reinnervation not only maintained the original level of capillarity associated with fast glycolytic fibres in control muscles, but considerably increased it. Thus long-term prazosin administration not only causes an increase in capillary supply in normal muscles but also prevents loss of capillaries during reinnervation. The fact that it only increases capillarisation in tissues where it increases flow further supports the hypothesis that capillary growth can be initiated by mechanical factors connected with high blood flow.

Key words: Capillary growth – Blood flow – Reinnervation

Introduction

It has been reported that drugs known to produce vasodilatation in the heart and skeletal muscle can induce capillary growth. Tornling et al. (1978) found decreased proliferation of capillaries in the heart after administration of dipyridamole, which is known to increase coronary blood flow (Winbury et al. 1971). Increased capillarisation of the heart was also described by Mall et al. (1982) after long-term administration of ethanol. In skeletal muscles, growth of capillaries was demonstrated by Ljungqvist et al. (1984) in rats treated with dipyridamole, and Sillau and Philippi (1987) observed increased capillary supply after long-term administration of isoprenaline. Ziada et al. (1984) described increased density of capillaries (CD) in the heart and muscles of rabbits treated for 4 weeks with either adenosine or a xanthine derivative in doses that increased blood flow and conductance in both vascular beds. They suggested that mechanical factors connected with increased blood flow may be responsible for capillary growth. If this is true, capillary growth should be induced only in the tissues in which vasodilator drugs actually increase blood flow. Prazosin, which is an α_1-blocker, is supposed to increase blood flow in several organs in the periphery but not in the heart (Sheridan et al. 1980). We therefore tested the effect of short-term administration of prazosin on coronary and muscle blood flow to determine a dose which would increase the former but not the latter, and then ascertained whether chronic administration of prazosin would induce capillary growth in either organ.

Large and Tyler (1985) described a redistribution of capillaries along muscle fibres with different oxidative capacity during reinnervation: motor units composed of purely glycolytic fibres had a lower capillary density than that attributed to these fibres in normal mixed muscles. Experiments were performed to ascertain whether long-term administration of prazosin would prevent this relative decrease in CD by maintaining blood flow at high levels.

Materials and methods

Experiments were performed on male Sprague-Dawley rats. Mean body weights for rats drinking prazosin and water were 397 ± 18 g and 416 ± 22 g respectively (means $\pm$ SEM). Prazosin was infused into the jugular vein for 30 min in 8 animals to find a suitable dose that would increase blood flow in skeletal muscles. An equivalent dose was then given to 12 animals in their drinking water over a period of 5 weeks. The control group comprised 12 animals which only drank water. Finally, the effect of long-term administration of prazosin after crush on the peroneal nerve on capillary supply was investigated during reinnervation in 6 animals; these rats were slightly lighter (368 ± 11 g).

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Blood flow was measured in acute experiments using labelled 15 μm microspheres (New England Nuclear, Boston, MA, USA) under sodium pentobarbital anaesthesia (Sagatal, May and Baker, Pagenham, Essex, UK) given intraperitoneally (50 mg · kg^{-1} diluted 1:1 with saline). The trachea and jugular vein were cannulated and the animals were allowed to breathe spontaneously. Both brachial arteries were cannulated using polyethylene cannulae (pp 90 pulled out to about the half of the original diameter), one for measurement of blood pressure and the other for withdrawal of blood. The left ventricle was cannulated via the right carotid artery using a pulled-out nylon cannula (outer diameter 1.3 mm) to inject 15 μm microspheres and to monitor the left ventricular pressure. Microspheres ($125-250\times10^3$) labelled with ^{46}Sc, ^{113}Sn, ^{95}Nb or ^{141}Ce were diluted with saline to 0.9 ml, of which 0.7 ml was injected. Withdrawal rate was 0.5 ml · min^{-1}, using a 5-ml syringe and a Braun withdrawal pump. Samples of left ventricular free wall, lungs, kidneys and skeletal muscles [extensor digitorum longus (EDL) and tibialis anterior (TA)] were taken for the estimation of blood flow as described previously (Hudlicka et al. 1981). The activity of whole lungs was calculated to assess possible shunting, and right and left kidney flow was compared to assess the mixing of microspheres. The activity was measured on a gamma radiation counter (ICN Instruments, Belgium) for 1 min. Blood flow was expressed, after the necessary corrections of the activity for background and crossover radiation, in terms of ml · (100 g^{-1} tissue) · min^{-1}.

Administration of prazosin. Prazosin hydrochloride (Pfizer, Sandwich, UK) was disolved in distilled water to its maximal soluble concentration of 50 μg · ml^{-1} at room temperature. Different doses in acute experiments were achieved by using different speeds of the infusion pump (Braun, Melsungen, FRG), 0.01, 0.05 and 0.1 ml · min^{-1} to deliver 30, 150 and 300 μg · h^{-1} respectively. Blood flow was measured after the infusion of the drug for 30 min. For long-term use, prazosin was dissolved in drinking water (50 μg · ml^{-1}). The dose for long-term administration was estimated as equivalent to 30 μg · h^{-1} given intravenously on the basis of the total amount of prazosin consumed on average per rat per day. Rats drank about 45 ml · day^{-1} of the solution at a concentration of 50 μg · ml^{-1} prazosin. An allowance was made for the plasma bioavailability (i.e. the percentage of orally administered dose that reaches the systemic circulation in unchanged form). This is known to be 38% in the dog (Taylor et al. 1977) and 44–70% (mean 57%) in man (Bateman et al. 1979). Assuming the bioavailability in the rat is similar to that in dogs, the effective dose which reached the circulation would be 35.6 μg · h^{-1} if no waste took place. Twelve rats (4 rats per cage) received prazosin for 5 weeks. The solution was in 250-ml drinking bottles (2 bottles per cage) whose teats allowed the delivery of the content on suction only. Bottles were dailed filled with a fresh solution. Twelve rats of similar weight, drinking water, served as controls. The consumption of fluid was similar in both groups.

Crushing of the peroneal nerve. Lateral peroneal nerve was crushed unilaterally under fluothane anaesthesia (2% in 95% O_2 and 5% CO_2) and aseptic conditions; a small incision was made on the lateral side of the left leg. After recovery from anaesthesia, the completeness of denervation was tested by the disappearance of the toe spreading reflex (Gutmann 1942). The animals were left for 7 weeks to allow complete reinnervation to occur (Large and Tyler 1985), and prazosin was supplied in drinking water over this whole period. As prazosin acts via α_1-blockade, it was important to find out whether adrenergic innervation of skeletal muscle vessels remained intact after the nerve crush. This was checked in the TA muscle of one rat 10 days after the nerve crush, using the glycoxylic acid fluorescence method, which enables the visualisation of catecholamine-containing nerve fibres.

Estimation of CD. Blocks from the mid-belly of EDL and TA, and from two sites in the hearts (one providing transverse fibre profiles in the subendocardial, the other in the subepicardial region) were taken out at the end of each experiment, frozen in isopenthane cooled in liquid nitrogen and sectioned on a cryostat (12 μm). Sections were fixed in acetone at 4°C for 5 min and air-dried prior to staining for alkaline phosphatase using indoxyl-tetrazolium method (Ziada et al. 1984). This staining is specific for alkaline phosphatase in capillary endothelium and thus reveals all capillaries present in the tissue examined. Evaluation of heart CD was carried out by counting the number of capillaries within ten randomly chosen fields of area 0.0625 mm^2 for each subendocardium and subepicardium. In skeletal muscles, capillaries per fibre (C/F) ratio were estimated by counting the number of capillaries and fibres in 40 bundles (each about 25 muscle fibres) from each muscle. TA muscles from the animals with crushed nerves were serially sectioned and stained not only for alkaline phosphatase, but also for succinic dehydrogenase (Pearse 1968) and myosin ATPase (Brooke and Kaiser 1969) to evaluate CD with respect to different fibre types using the method of Gray and Renkin (1978).

Statistical analysis of all results was carried out using paired or unpaired Student's *t*-test as appropriate. The values are given as means ± SEM.

Results

Acute administration of prazosin

Prazosin was given intravenously in three different doses – 30, 150 and 300 μg h^{-1} to find out which dose would increase skeletal muscle but not coronary blood flow. After 30 min of administration, all three doses resulted in a dose-dependent decrease in blood pressure, but none changed the heart rate (Table 1). Blood flow in skeletal muscles almost trebled with the lowest dose (Table 2), while the increase in blood flow with higher doses was smaller. However, because of a low blood pressure, the conductance in skeletal muscles increased by 430% and 520% with the two higher doses. Mean left ventricular blood flow and conductance in the heart were not significantly changed with either dose. On the basis of these results the lowest dose was selected for long-term administration.

Chronic administration of prazosin

Effect on body weight, heart rate and blood pressure. The gain in weight in rats drinking prazosin was similar (110 ± 19 g) to that in the control group (136 ± 11 g) over the period of 5 weeks. Heart rate and mean blood pressure were measured in three control animals and three prazosin-treated animals

Table 1. Effects of prazosin infusion (30, 150, 300 μg · h^{-1}) for 30 min on mean blood pressure and heart rate

Parameter measured	Value with prazosin infusion at								
	30 μg · h^{-1} ($n = 8$)			150 μg · h^{-1} ($n = 7$)			300 μg · h^{-1} ($n = 3$)		
	Rest	During infusion	cf resting (%)	Rest	During infusion	cf resting (%)	Rest	During infusion	cf resting (%)
Mean blood pressure (mm Hg)	117 ± 9.0	78 ± 8.0**	66.5 ± 5.5	119 ± 10.3	61 ± 6.2*	49.5 ± 3.9	147 ± 7.0	55 ± 10.0*	37.3 ± 5.9
Heart rate (beats · min^{-1})	382 ± 16.0	414 ± 16.0	109.6 ± 5.6	386 ± 17.9	417 ± 26.0	110.1 ± 10.3	403 ± 30.6	380 ± 9.0	95.5 ± 8.3

Values are mean ± standard error. * $P < 0.01$ vs resting; ** $P < 0.001$ vs resting

Table 2. Effect of prazosin infusion (30, 150, 300 μg · h^{-1}) for 30 min on skeletal muscle (EDL and TA) and mean left ventricular blood flow (BF) and conductance

Parameter measured	Value with prazosin infusion at								
	30 μg · h^{-1} ($n = 8$)			150 μg · h^{-1} ($n = 7$)			300 μg · h^{-1} ($n = 3$)		
	Rest	During infusion	cf resting (%)	Rest	During infusion	cf resting (%)	Rest	During infusion	cf resting (%)
Skeletal muscle BF (ml · min^{-1} · 100 g^{-1})	8.37 ± 1.55	19.69 ± 3.78*	281.8 ± 62.3	8.81 ± 1.71	18.87 ± 4.40*	254.1 ± 66.2	7.98 ± 0.49	16.44 ± 7.4	195.4 ± 85.8
Skeletal muscle conductance (ml · min^{-1} · g^{-1} · mm Hg) × 10^{-5}	75.125 ± 17.687	263.125 ± 52.460**	437.1 ± 100.164	78.286 ± 20.095	359.286 ± 114.507*	534.8 ± 148.0	54.667 ± 5.608	363.333 ± 180.546	617.7 ± 310.3
Left ventricular BF (ml · min^{-1} · 100 g^{-1})	404.2 ± 63.2	271.9 ± 64.0	76.4 ± 16.5	379.5 ± 67.3	303.5 ± 40.1	98.4 ± 24.8	451.1 ± 116.0	359.1 ± 136.3	76.0 ± 26.8
Left ventricular conductance (ml · min^{-1} · g^{-1} · mm Hg^{-1}) × 10^{-5}	3,597 ± 627	3,970 ± 1,239	116.8 ± 22.8	3,281 ± 625	5,542 ± 1,103	210 ± 62.5	3,161 ± 968	7,794 ± 3,530	242.2 ± 122.0

* $P < 0.05$ vs resting; ** $P < 0.01$ vs resting

3 h after the administration of prazosin had ceased. The results were similar in both groups – the mean blood pressure 120 ± 17 mm Hg in the control and 123 ± 8 mm Hg in the group on prazosin respectively. Heart rate was 460 ± 10 beats · min^{-1} in control animals and 420 ± 30 beats · min^{-1} in those on prazosin.

Heart weight and myocardial CD. Since CD is very much related to the fibre cross-section area and hence to the size of the heart, heart and heart/body weight ratio (H/B) were compared in control rats and animals on prazosin. The mean heart weight was 1.135 ± 0.077 g in control animals and 1.102 ± 0.092 g in those drinking prazosin. The H/B weight ratio was 0.280 ± 0.004 in 11 prazosin-treated rats and 0.279 ± 0.006 in 11 control animals. CD was similar in both subendocardial (2,504 ± 182 mm^{-2} vs 2,608 ± 133 mm^{-2}) and subepicardial (2,622 ± 153 mm^{-2}, vs 2,681 ± 107 mm^{-2}) layers in control and treated animals, and there was no significant difference in the mean capillary density between the two groups, i.e. 2,582 ± 157 mm^{-2} vs 2,644 ± 113 mm^{-2} for water and prazosin drinking rats respectively (Fig. 1).

CD in skeletal muscles. Since capillary density in skeletal muscle varies with fibre size and types, C/F ratio was used as an estimate of capillary proliferation. C/F ratio in EDL, estimated in 12 prazosin-treated and 9 control muscles was

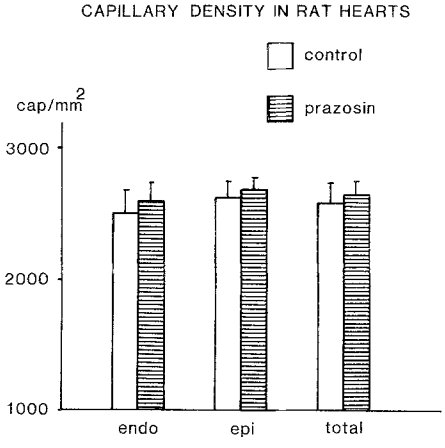

Fig. 1. Capillary density in rat hearts after administration or prazosin

1.69 ± 0.01 and 1.52 ± 0.019 respectively ($P < 0.001$). The respective values in 4 TA muscles from each group were 2.16 ± 0.04 and 1.52 ± 0.019. TA has a peripheral cortex composed predominantly of glycolytic fibres while the core of the muscle is oxidative. Separate estimation of C/F ratio in these two regions showed a similar increase in the core (from 1.837 ± 0.14 to 2.51 ± 0.12, $P < 0.005$) and cortex

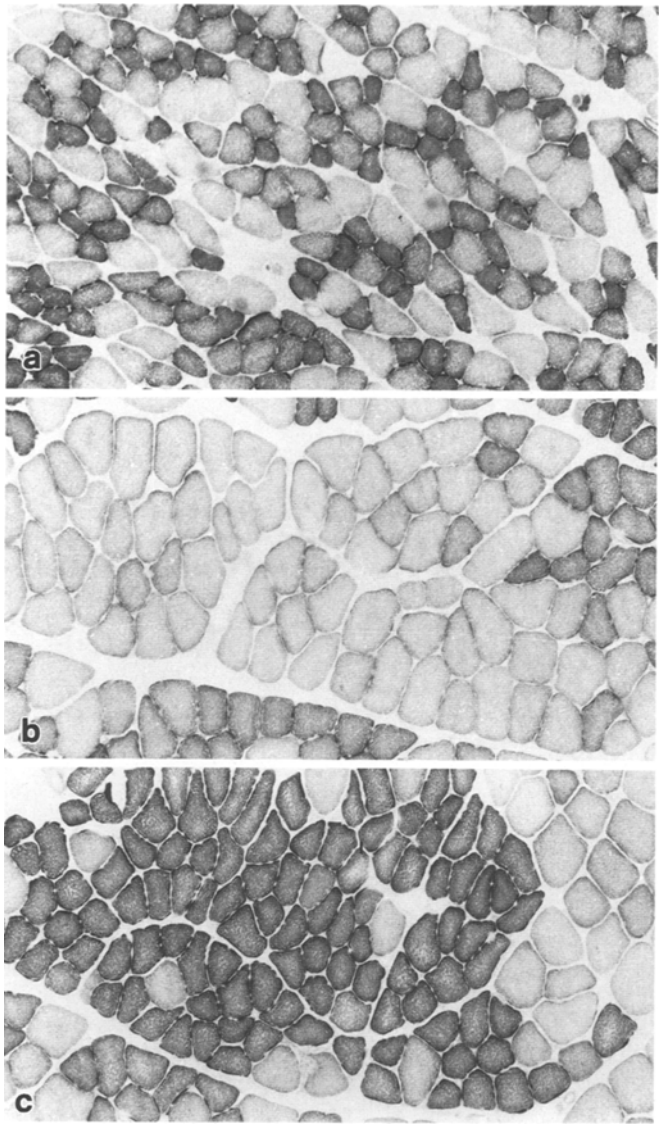

Fig. 2. Cross-section from the outer part of the cortex of tibialis anterior (TA) stained for succinic dehydrogenase SDH; (**a**) control muscle (**b**) reinnervated TA with glycolytic fibre grouping (**c**) oxidative fibre grouping. Darkly stained fibres are oxidative

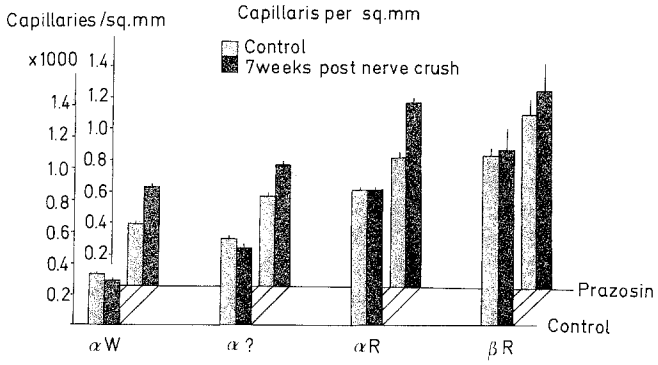

Fig. 3. Capillary density in control and reinnervated muscle from control rats and rats that had been drinking prazosin. αW, Fast glycolytic fibres; αR, fast oxidative fibres; βR, slow oxidative fibres; $\alpha ?$, intermediate fibres; classified according to Gray and Renkin (1978)

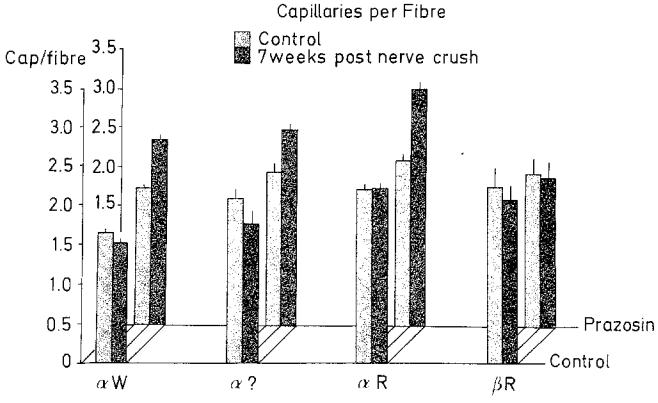

Fig. 4. Capillaries per fibre (C/F) ratio in control and reinnervated muscles from control and prazosin-treated rats. Same details as in Fig. 3

(from 1.30 ± 0.13 to 1.75 ± 0.11, $P < 0.025$). In reinnervated muscles, fibres became redistributed from the typical mosaic pattern, best expressed in the outer part of the core, into groups of adjacent fibres of similar oxidative cavity (Fig. 2). Seven weeks after nerve crush, the weight of reinnervated TA was similar to that of control muscle (0.890 ± 0.04 g and 0.823 ± 0.042 g respectively). Fibre cross-sectional areas, estimated from 200 fibres in each group, were larger in reinnervated ($2{,}730 \pm 231$ μm^2) than in control muscles ($2{,}151 \pm 124$ μm^2) ($P < 0.05$) for fast oxidative fibres and not significantly different in the other fibre groups – $1{,}439 \pm 48 \mu m^2$ vs $1{,}676 \pm 192$ μm^2 for slow oxidative, $3{,}579 \pm 210$ μm^2 vs $3{,}404 \pm 202$ μm^2 for intermediate fibres and $4{,}299 \pm 266$ μm^2 vs $4{,}791 \pm 363$ μm^2 for glycolytic fibres in the reinnervated and control muscles respectively. Capillary supply expressed as capillaries · mm^{-2} or C/F ratio was lowest in the areas was fast glycolytic fibres and highest in the fast oxidative fibres. Reinnervated muscles of prazosin-treated rats had considerably higher CD and C/F ratio in all fast fibre groups (Figs. 3, 4) than intact muscles. Thus administration of prazosin prevented the loss of capillaries in glycolytic areas as previously described in reinnervated muscles (Large and Tyler 1985).

Discussion

All estimations of capillary supply in this study are based on a specific staining of capillary endothelium for alkaline phosphatase. Thus counting of the stained profiles depicts all capillaries anatomically present, and an increase in the number of profiles strongly indicates growth of capillaries. This growth was confirmed in chronically stimulated muscles by measurements of CD, C/F ratio and total capillary length in electron micrographs (Hudlicka et al. 1987) and by a correlation of both histochemical staining for capillaries and C/F ratio with the incidence of capillary sprouts observed in vivo (Myrhage and Hudlicka 1978). Capillary proliferation – or the lack of it – can thus be assessed by the change in either CD (number of capillaries · mm^{-2}), or C/F ratio. The first parameter was used in the heart, since the delineation of muscle fibres did not allow an accurate estimation of C/F ratio. The second parameter was used in skeletal muscle because it is less dependent on fibre area

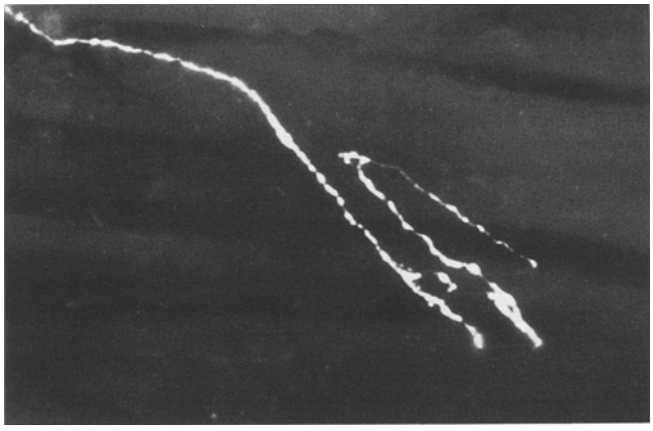

Fig. 5. Adrenergic nerve in TA 10 days after nerve crush depicted with the glycoxylic method. These fibres can be seen as string-like structures accompanying a vessel oriented transversely to the muscle fibres

(Hudlicka 1985). Plyley and Groom (1975) and Banchero and his collaborators (Loats et al. 1977; Sillau and Banchero 1978; Ripoll et al. 1979) showed that CD in skeletal muscles is increasingly higher in progressively smaller muscle fibres; Hakkila (1955) and Wright and Hudlicka (1981) showed a similar relationship in the heart.

Prazosin administered orally over a period of several weeks did not affect CD in the rat heart. An unchanging CD in the absence of differences in heart weight and H/B ratios clearly indicates lack of capillary growth. Increased C/F ratio in TA and, though to a smaller extent, in EDL clearly indicates growth of capillaries in skeletal muscle. Detailed analysis of the TA showed that this increase was localised in all groups of fast fibres; since slow fibres in this muscle represent only 2% of the total fibre population (Ariano et al. 1973; Armstrong and Phelps 1984), the increase in the capillarity was distributed throughout the whole muscle. Since the method used for visualisation of capillaries in this study specifically stains capillary endothelium, all capillaries present in the tissue are depicted whether perfused or not. Therefore, an increase in C/F ratio must mean the new capillaries have been formed, provided that the tortuosity was not so great that one capillary would be sectioned twice in the same cross section (Appell 1984). Mathieu et al. (1983) have shown that this is not likely to be the case in soleus – a muscle with the greatest degree of capillary tortuosity (Hammersen 1964). She and her co-workers (Poole et al. 1989) also showed a dependence of the tortuosity of capillaries on sarcomere length; however, neither CD estimated from cross-sections, nor C/F ratio in their experiments showed any linear correlation with sarcomere length. Since capillaries in both EDL and TA are straight, it is unlikely that our results would be affected by sarcomere length.

The mechanism possible for proliferation of capillaries in skeletal muscles, and its absence in the heart, could be connected with the effects of prazosin on blood flow – flow was trebled in skeletal muscles, but not significantly changed in the heart. C/F ratio increased by 30% in TA and by 11% in EDL. This is not proportional to the increase in flow, but still represents a considerable increase in C/F ratio in TA not previously described using other dilators. Tornling (1982) found a 22% higher C/F ratio in skeletal muscles of rats treated for 3 weeks by dipyridamole, and Ziada et al. (1984) described a higher C/F in rabbit muscles treated for 3–5 weeks with adenosine (25%) or the xanthine derivative HWA 285 (22%). While there are no data on blood flow in Tornling's experiments, the data from our previous work (Ziada et al. 1984) showed an increase in flow of 65% with adenosine and 41% with HWA 285. All drugs causing dilatation could have a direct effect on capillary growth through various mechanical factors associated with increased blood flow, e.g. greater red cell flux or velocity, increased capillary pressure and wall tension or greater shear stress (Hudlicka and Tyler 1986; Hudlicka 1988), or they could have an indirect effect on endothelial cell metabolism. This latter effect is less likely in the case of dipyridamole, which did not cause any proliferation of the endothelial cells in tissue cultures (Jacob et al. 1982), but cannot be excluded in cases of adenosine or HWA 285. Small doses of adenosine stimulated incorporation of [^{3}H]thymidine into lymphocytes (Carson and Seegmiller 1976) whilst xanthines increased endothelial cell proliferation in vitro (Davison and Karasek 1981). There are no data on any direct metabolic effect of prazosin on vascular endothelium. However, it increased the velocity of RBC and diminished the intermittency of flow (Dawson and Hudlicka 1987), and it is thus likely that it can stimulate capillary growth by mechanical factors mentioned above.

Prazosin produces dilatation by blocking α_1-receptors. Consequently, it cannot be expected that its administration would produce a great change in the coronary vascular bed, and indeed neither coronary blood flow nor conductance or CD were changed. The diverse effects of prazosin in the heart and skeletal muscle strongly support the assumption that mechanical factors connected with increased blood flow are stimulating capillary proliferation.

Further evidence for the above hypothesis is provided by the experiments on reinnervated muscles. Reinnervation is known to result in the production of groups of adjacent fibres of very similar histochemical characteristics that presumably belong to single motor units (Karpati and Engel 1968; Kugelberg et al. 1970). Large and Tyler (1985) described a significantly lower CD in the areas formed by fast glycolytic fibres (284 ± 18 min^{-2}) than that attributed to those fibres in a normal mixed muscle (322 ± 20 mm^{-2}). Long-term administration of prazosin increased CD in these areas to 631 ± 14 mm^{-2} – almost double the value found in control muscles. Since the fibre areas were similar, this increase again demonstrates capillary proliferation.

The increase in blood flow during administration of prazosin is, of course, dependent on the block of α_1 adrenergic fibres. Some of them, accompanying the peripheral nerves, could be damaged during the nerve crush. We therefore tested their presence in TA 10 days after the nerve crush, during the initial period of reinnervation (Fig. 5). Figure 5 shows presence of adrenergic fibres along the vessels in TA at this time. These fibres might have been running parallel to larger vessels in the femoral nerve or elsewhere due to the regeneration of some fibres in the peroneal nerve.

Thus the increased blood flow prevents the loss of capillaries found in areas of glycolytic fibres after reinnervation. The flaccidity of the limb before the full functional operation is restored might also reduce the occluding effect of contracting muscles on the vessel wall, and thus enhance the increase in blood flow produced by prazosin administration. Whatever the mechanism, this combined effect of a great increase

in blood flow resulted in a great proliferation of capillaries homogeneously distributed throughout the muscle, and seems to support the hypothesis that a longlasting increase in blood flow can induce capillary proliferation.

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References

Appell H-J (1984) Variability in microvascular pattern dependent upon muscle fiber composition. Prog Appl Microcirc 5:15–29

Ariano MA, Armstrong RB, Edgerton VR (1973) Hindlimb muscle fiber populations of five mammals. J Histochem Cytochem 21:51–55

Armstrong RB, Phelps RO (1984) Muscle fibre type composition of the rat hindlimb. Am J Anat 171:259–272

Bateman DN, Hobbs DC, Twomey TM, Stevens EA, Rawlins MD (1979) Prazosin pharmacokinetics and concentration effect. Eur J Clin Pharmacol 16:177–181

Brooke MH, Kaiser KK (1969) Some comments on the histochemical characterization of muscle adenosine trisphosphates. J Histochem Cytochem 17:431–432

Carson DA, Seegmiller JE (1976) Effect of adenosine deaminase inhibition upon human lymphocyte blastogenesis. J Clin Invest 57:274–282

Davison PM, Karasek MA (1981) Human dermal microvascular endothelial cells in vitro. Effect of cyclic AMP on cellular morphology and proliferation rate. J Cell Physiol 106:253–258

Dawson JM, Hudlicka O (1987) Adaptations of the rat microvasculature to long-term administration of prazosin. J Physiol (Lond) 387:71P

Gray SD, Renkin EM (1978) Microvascular supply in relation to fibre metabolic type in mixed skeletal muscle of rabbit. Microvasc Res 16:406–425

Gutmann E (1942) Factors affecting recovery of motor function after nerve lesions. J Neurol Neurosurg Psychiatry 5:81–95

Hakkila J (1955) Studies on the myocardial capillary concentration in cardiac hypertrophy due to training. Ann Med Exp Biol Fenn 33 [Suppl 10]:1–82

Hammersen F (1964) Das Gefässmuster der Skelettmuskulatur. Probleme der Haut- und Muskeldurchblutung. Bad Oeynhausener Gespräche 6:11

Hudlicka O (1985) Development and adaptability of microvasculature in skeletal muscle. J Exp Biol 115:215–228

Hudlicka O (1988) Capillary growth: role of mechanical factors. NIPS 3:117–120

Hudlicka O, Tyler KR (1986) Angiogenesis. Academic Press, London

Hudlicka O, Komarek J, Wright AJA (1981) The effect of a xanthine derivative, 1-(5′oxohexyl)-3-methyl-7-propylxanthine (HWA 285) on heart performance and regional blood flow in dogs and rabbits. Br J Pharmacol 72:723–730

Hudlicka O, Hoppeler H, Uhlmann E (1987) Relationship between the size of the capillary bed and oxidative capacity in various cat skeletal muscles. Pflügers Arch 410:369–375

Jacob W, Zipper J, Savoly SB, Siems W-E, Jentzsch KO (1982) Is dipyridamole an angiogenic agent? Exp Pathol 22:217–224

Karpati G, Engel WK (1968) 'Type grouping' in skeletal muscles after experimental reinnervation. Neurology 18:447–455

Kugelberg E, Edström L, Abbruzzese M (1970) Mapping of motor units in experimentally reinnervated rat muscle. J Neurol Neurosurg Psychiatry 33:319–329

Large J, Tyler KR (1985) Changes in capillary distribution in rat fast muscles following nerve crush and reinnervation. J Physiol (Lond) 362:13–21

Ljungqvist A, Tornling G, Unge G, Jurdahl EB, Larsson B (1984) Capillary growth in the heart and skeletal muscle during dipyridamole treatment and exercise. Prog Appl Microcirc 4:9–15

Loats JT, Sillau AH, Banchero N (1977) How to quantify skeletal muscle capillarity. Adv Exp Med Biol 94:41–48

Mall G, Mattfeldt T, Rieger P, Volk B, Frolov VA (1982) Morphometric analysis of the rabbit myocardium after chronic ethanol feeding – early capillary changes. Basic Res Cardiol 77:57–67

Mathieu O, Cruz-Orive L-M, Hoppeler H, Weibel ER (1983) Estimating length density and quantifying anisotropy in skeletal muscle capillaries. J Microsc 131:131–146

Myrhage R, Hudlicka O (1978) Capillary growth in chronically stimulated adult skeletal muscle as studied by intravital microscopy and histological methods in rabbits and rats. Microvasc Res 16:73–90

Pearse AGE (1968) Histochemistry – theoretical and applied, vol 1, 3rd edn. Churchill Livingstone, Edinburgh, London New York

Plyley MJ, Groom AC (1975) Geometrical distribution of capillaries in mammalian striated muscle. Am J Physiol 228:1376–1383

Poole DC, Mathieu-Costello O, West JB (1989) Capillary tortuosity in rat soleus muscle in not affected by endurance training. Am J Physiol 256:H1110–H1116

Ripoll E, Sillau AH, Banchero N (1979) Changes in the capillarity of skeletal muscle in the growing rat. Pflügers Arch 380:153–158

Sheridan DM, Penkoske PA, Burton ES, Corr PB (1980) Alpha adrenergic contributions to dysrhythmia during myocardial ischaemia and reperfusion in cats. J Clin Invest 65:161–171

Sillau AH, Banchero N (1978) Skeletal muscle fibre size and capillarity. Proc Soc Exp Biol Med 158:288–291

Sillau AH, Philippi ML (1987) Long-term isoprenaline administration produces an increase in capillarity in the soleus muscle of the rat. Can J Physiol Pharmacol 65:303–306

Taylor JA, Twomey ZM, Schach von Wittenau M (1977) The metabolic fate of prazosin. Xenobiotica 7:357–364

Tornling G (1982) Capillary neoformation in the heart and skeletal muscle during dipyridamole-treatment and exercise. Acta Pathol Microbiol Scand [A] [Suppl] 278:5–57

Tornling G, Unge G, Skoog L, Ljungqvist A, Carlsson S, Adolfsson J (1978) Proliferative activity of myocardial capillary wall cells in dipyridamole treated rats. Cardiovasc Res 12:692–695

Winbury MM, Howe BB, Weiss HR (1971) Effect of nitroglycerin and dipyridamole on epicardial and endocardial oxygen tension – further evidence for redistribution of myocardial blood flow. J Pharmacol Exp Ther 176:184–199

Wright AJA, Hudlicka O (1981) Capillary growth and changes in heart performance induced by chronic bradycardial pacing in rabbits. Circ Res 49:469–478

Ziada AMAR, Hudlicka O, Tyler KR, Wright AJA (1984) The effect of long-term vasodilatation on capillary growth and performance in rabbit heart and skeletal muscle. Cardiovasc Res 18:724–732

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