Myogenic Tone in Isolated Perfused Vessels

OCCURRENCE AMONG VASCULAR BEDS AND ALONG VASCULAR TREES

By Eiichi Uchida, M.D., and David F. Bohr, M.D.

ABSTRACT

In situ studies yield only indirect evidence as to whether non-neurogenic vascular tone results from an intrinsic myogenic tendency of the smooth muscle cell to contract or is due to stimulation of the muscle by some vasoactive humoral influence of the environment. In the current study, small resistance vessels from different vascular beds, from various levels of the arterial tree, and from several species were isolated and perfused with physiological salt solution. Under these conditions the environment is devoid of any vasoactive, in-situ, humoral influence, and tonic contraction would have to be of myogenic origin. Myogenic tone was consistently present in smooth muscle from some vascular beds, whereas it was absent from other beds. Myogenic tone was more prevalent in smaller vessels (50 to 100 μ o.d.) than in larger ones (100 to 400 μ o.d.). Significant differences in this property were observed among the species studied. We conclude that, contrary to the properties classically assigned it as a multiunit smooth muscle, most vascular smooth muscle from resistance vessels is intrinsically and spontaneously active.

ADDITIONAL KEY WORDS

vascular smooth muscle
peripheral circulation resistance vessels calcium and muscle contraction
intrinsic tone dogs rats rabbits monkeys

In a previous paper dealing with isolated perfused vessels (1), we described two types of resistance vessels: those from rat skeletal muscle that have spontaneous myogenic tone and those from rat mesentery that do not. Because this difference is so consistent and so great it must be a significant basis for individuality in the regulation of the various peripheral vascular beds (2).

In the present study we examined the distribution of myogenic tone in isolated resistance vessels from different sites in the body and its existence at various levels of the arterial tree and among different species.

Methods

Materials.—Fifty-four Sprague-Dawley rats (240 to 353 g), 12 New Zealand rabbits (2.3 to 4.3 kg), 12 mongrel dogs (13 to 16 kg), and 5 rhesus monkeys (7 to 9 kg) were used. All animals, except one monkey, were males. Rats and rabbits were usually killed by a blow on the head, but when cerebral arteries were to be taken, rats were killed by decapitation and rabbits by intravenous injection of pentobarbital sodium, which was also the method of killing dogs and monkeys.

In all species, resistance vessels to be perfused were from a branch of the superior mesenteric artery in the mesojejunum, a branch of the femoral artery in the skeletal muscle, and a branch of the middle cerebral artery. In rats, other vessels also were studied: a branch of the coronary artery, a branch of the intrarenal artery, a branch of the superficial epigastric artery in subcutaneous tissue, and minute vessel branches within the intestinal wall. Numbers of preparations are listed in Table 1.

From the Department of Physiology, University of Michigan, Ann Arbor, Michigan 48104.

This study was supported in part by U. S. Public Health Service Grant HE-03756 from the National Heart Institute.

Dr. Uchida's travel funds were provided by a U. S. Government grant, authorized under the Fulbright-Hayes Act. His permanent address is The Cardiovascular Institute, 8-1-22 Akasaka, Minato-ku, Tokyo, Japan.

Received May 19, 1969. Accepted for publication September 8, 1969.
TABLE 1

Occurrence of Myogenic Tone in Resistance Vessels of Various Vascular Beds

<table>
<thead>
<tr>
<th>Location of vessel</th>
<th>Vessel size (μ m o.d.)</th>
<th>No. with tone</th>
<th>No. without tone</th>
<th>Tone as % of total resistance*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>80-320</td>
<td>0</td>
<td>14</td>
<td>30-85</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>80-320</td>
<td>70</td>
<td>0</td>
<td>20-26</td>
</tr>
<tr>
<td>Brain</td>
<td>100</td>
<td>2</td>
<td>0</td>
<td>14-64</td>
</tr>
<tr>
<td>Heart</td>
<td>100-240</td>
<td>3</td>
<td>0</td>
<td>14-64</td>
</tr>
<tr>
<td>Kidney</td>
<td>120-240</td>
<td>2</td>
<td>1</td>
<td>18-19</td>
</tr>
<tr>
<td>Subcutaneous tissue</td>
<td>120-200</td>
<td>3</td>
<td>0</td>
<td>17-52</td>
</tr>
<tr>
<td>Rabbit</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>100-320</td>
<td>0</td>
<td>9</td>
<td>9-38</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>120-280</td>
<td>3</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Brain</td>
<td>80-240</td>
<td>0</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Dog</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>160-280</td>
<td>0</td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>160-320</td>
<td>3</td>
<td>1</td>
<td>7-20</td>
</tr>
<tr>
<td>Brain</td>
<td>60-300</td>
<td>9</td>
<td>11</td>
<td>11-52</td>
</tr>
<tr>
<td>Monkey</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mesentery</td>
<td>200-320</td>
<td>1</td>
<td>3</td>
<td>47</td>
</tr>
<tr>
<td>Skeletal muscle</td>
<td>140-280</td>
<td>6</td>
<td>0</td>
<td>14-53</td>
</tr>
<tr>
<td>Brain</td>
<td>80-320</td>
<td>13</td>
<td>0</td>
<td>11-70</td>
</tr>
</tbody>
</table>

*The part myogenic tone plays in total resistance is calculated as:

\[
\frac{\text{Total resistance} - \text{Structural resistance}}{\text{Total resistance}} \times 100.
\]

Preparation and Perfusion.—Preparation of the vessels and the method of perfusion have been described in detail (3). A part of the arterial tree was isolated from its surrounding tissue and a section of the vessel prepared for perfusion by tying off all branches except the terminal one. The vessel segment was cannulated at its proximal end and mounted in a muscle chamber. The perfusion fluid, warmed (37°C) and aerated (95% O₂, 5% CO₂) physiological salt solution entered through the cannula and flowed out through the free terminal branch into the muscle chamber. A constant flow rate was maintained by a modified Sigma motor pump. Perfusion pressure was recorded by a pressure transducer, through the side arm of the cannula. Flow rate was recorded as the rate of increasing volume of outflow from the muscle chamber into an automatically emptying glass tube. Tracings from the experiments can be seen in Figure 1. Since perfusion was at constant flow rate, a rise in perfusion pressure indicates an increase in resistance (vasoconstriction), and a fall in perfusion pressure indicates a decrease in resistance (vasodilatation).

Solutions and Drugs.—The composition of the basic perfusion fluid, physiological salt solution, in millimoles per liter, was: NaCl, 119.0; KCl, 4.7; KH₂PO₄, 1.18; MgSO₄·7H₂O, 1.17; NaHCO₃, 14.9; dextrose, 5.5; sucrose, 50.0; CaCl₂, 1.6; and CaNa₂ versenate, 0.026. “Ca-free” solution had no CaCl₂.

The pharmacological agents used were: norepinephrine (Levophed, Winthrop), epinephrine (adrenalin chloride solution, Parke, Davis & Co.), sodium nitrite (crystal, Allied Chemical Co.), hydralazine HCl (Apresoline, Ciba), and papaverine HCl (papaverine hydrochloride injection, NF, Win. S. Merrell Co.).

Experimental Procedures.—An initial perfusion period of 1 to 2 hours was allowed for stabilization of the preparation before experimental procedures were begun. The environment of the vessel was changed by switching to the perfusion fluid of an alternate aerating chamber, and simultaneously changing the solution in the bath by a flushing system attached to the muscle chamber. All pharmacological agents were injected into the perfusion fluid by a microinjector system as previously described (3).

Results

Evidence of Myogenic Tone in Some Resistance Vessels.—Previously we described intrinsic myogenic tone in resistance vessels (100 to 320 μ m o.d.) from rat skeletal muscle (1). In the current study we found that the
rat coronary vessel also has myogenic tone, as demonstrated in Figure 1A by (1) a gradual increase in perfusion pressure with time after starting perfusion; (2) a large drop in pressure during perfusion with Ca-free physiological salt solution; and (3) vasodilatation by vascular smooth muscle relaxants such as isoproterenol and papaverine (150 μg of papaverine caused a decrease in perfusion pressure to its level during Ca-free perfusion). The residual pressure during Ca-free perfusion or after injection of a supramaximal dose of sodium nitrite, hydralazine, or papaverine represents the passive, structural resistance of the vessel (1). The magnitude of the decrease in perfusion pressure reflects the amount of intrinsic myogenic tone.

Evidence of Lack of Tone in Some Resistance Vessels.—Resistance vessels from rat mesenteric vasculature had no demonstrable myogenic tone, nor did those from rabbit mesentery. Figure 1B shows evidence of lack of tone in a mesenteric artery from a rabbit.

Although these mesenteric vessels did not constrict spontaneously, they were capable of a strong constriction in response to an injection of epinephrine, norepinephrine, or potassium chloride.

Occurrence of Resistance Vessels with and without Myogenic Tone.—Table 1 summarizes the occurrence of resistance vessels with and without myogenic tone in the various vascular beds examined. The presence of myogenic tone in resistance vessels (80 to 320 μ o.d.) depends both on the part of the body from which the vessel was obtained and on the species of animal.

Occurrence of Myogenic Tone at Different Levels of the Arterial Tree.—An attempt was made to estimate the magnitude of the myogenic tone at various levels of the arterial tree in systems in which a part of the total resistance was due to active contraction. Studies were also carried out to determine whether there was myogenic tone in branches
Along the vascular tree (muscle branch of femoral artery) the magnitude of the myogenic tone, as evidenced by the amount of relaxation in a Ca-free environment, is inversely proportional to the diameter of the smallest part of the perfused vessel. Inset shows where successive cuts were made to provide terminal segments of successively greater diameter.

**TABLE 2**

<table>
<thead>
<tr>
<th>First branch</th>
<th>Second branch</th>
<th>Third branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Size (µ o.d.)</td>
<td>% of total resistance*</td>
<td>Size (µ o.d.)</td>
</tr>
<tr>
<td>320</td>
<td>42</td>
<td>240</td>
</tr>
<tr>
<td>260</td>
<td>32</td>
<td>200</td>
</tr>
<tr>
<td>320</td>
<td>52</td>
<td>140</td>
</tr>
</tbody>
</table>

*See footnote, Table 1.

distal to the vessels that were devoid of myogenic tone. (See Figure 2 and Table 2.)

Parts of the femoral arterial tree other than the usual muscle branches were also perfused and examined for myogenic tone in 6 rats (Fig. 3). In muscle branches (140 to 240µ), over 50% of the resistance was attributable to myogenic tone; in branches of the tibial artery (120 to 240µ), approximately 50%, and in branches of the popliteal (160µ), approximately 40%. Trunk arteries, femoral (400µ), saphenous (300 to 400µ) and superior epigastric (480µ), had no demonstrable myogenic tone.

Although rat mesenteric artery is without myogenic tone, sections of very small branches of this artery (60 to 100µ o.d., 5 of 9 preparations) from within the intestinal wall did have myogenic tone, ranging from 27% to 51% of the total resistance (Table 3). These vessels met the criteria required to establish the existence of myogenic vascular tone (Fig. 4).

**Discussion**

The goal of this study was to map the occurrence of myogenic tone in segments of resistance vessels from different vascular beds, from various levels of the arterial tree, and from several species. The appropriateness of...
Considering vessels of the size studied “resistance vessels” has been discussed previously (4). Although the results of this survey are best perceived by a study of the distribution data (Table 1), three generalizations emerge that merit emphasis:

1. Resistance vessels from certain areas tend to have myogenic tone, those from other areas do not, and this is independent of species. The resistance vessels of skeletal muscle most consistently have this intrinsic contractile property; resistance vessels in the mesentery very seldom do. Cerebral resistance vessels usually have myogenic tone, but it is less than that of resistance vessels from skeletal muscle.

2. There is a tendency for small resistance vessels (50 to 100\(\mu\) o.d.) to have more myogenic tone than larger vessels (100 to 400\(\mu\) o.d.) (Fig. 3). This generalization appears to be valid even though it is virtually impossible to measure the degree of vascular smooth muscle contraction in vessels of different sizes when resistance is used as an index of contractility. The reason for this difficulty is that there is not a one-to-one relationship between change in muscle length and change in resistance (this refers to the large exponential value of Poiseuille’s equation). Furthermore, there is no way of determining how much of a contraction is a shortening of the smooth muscle cell and how much is an increase in tension. This latter problem is relevant because of the change in tension in the wall as the perfusion pressure rises in response to an increase in vascular resistance downstream. This increase in tension will obviously vary with the size of the vessel (LaPlace’s law). In spite of these objections, the generalization that tone is greater in smaller vessels is suggested by the greater percent of active to structural resistance in these vessels. That tone is less in the larger vessels is substantiated by two observations: (a) The large conduit vessels in the femoral area have no myogenic tone, even in the rat, in which all muscle branches of this system do (Fig. 3). (b) Although small mesenteric arteries of the rat are without myogenic tone, their distal extensions into the wall of the intestine do develop it (Table 3). This observation, that the amount of myogenic tone is greater in resistance vessels of less than 100\(\mu\) o.d., raises the possibility that this property of vascular smooth muscle may exist in all vascular beds in vessels too small (less than 50\(\mu\) o.d.) to be studied with the present technique.

3. There are species individualities in the display of myogenic tone. Of the four species studied, myogenic tone appears to be most prominent in the rat and least prominent in the rabbit. It is tempting to relate this observation to the recognized stability of the
Distribution of ability to develop myogenic tone along mesenteric arterial tree (vessel without myogenic tone). A, There is no evidence of myogenic tone in mesenteric resistance vessels 200 µ o.d. B, Arterioles 80 µ o.d. in the intestinal wall show evidence of myogenic tone in initial increase in pressure, fall in pressure, when perfusion fluid is shifted from normal to Ca-free physiological salt solution, fall in pressure with isoproterenol (IP) and papaverine.

The results of this study have relevance to two important physiological principles.

1. Most resistance vessels, except those from the rabbit, have a considerable amount of intrinsic myogenic tone. From this observation it can be inferred that this property of vascular smooth muscle may be responsible for an important component of total peripheral resistance, and since its magnitude varies from one vascular bed to another, it may play some role in determining distribution of blood flow.

2. Although most vascular smooth muscle remains partially contracted after denervation in the intact animal (5), only indirect evidence from these in-situ studies indicates whether this non-neurogenic vascular tone is due to an intrinsic, myogenic tendency of the smooth muscle cell to contract, or whether it is due to stimulation of the muscle by some vasoactive humoral influence of the environment in situ. This indirect evidence has given the strong impression that non-neurogenic tone is primarily of myogenic origin (6). It has been shown (7) that in acutely sympathectomized and adrenalectomized cats the precapillary resistance vessels of skeletal muscle have non-neurogenic vascular tone, whereas those of the skin, in the same animal, perfused with the same blood, are maximally relaxed. Since it was also observed that the cutaneous vessels are more responsive to blood-borne humoral agents than are those in skeletal muscle, it seems reasonable to conclude that precapillary resistance tone in skeletal muscle vessels is strictly of local origin. This does not exclude the possibility of
local production of a constrictor agent by nonmuscular cells in the vessel wall. However, this unlikely possibility is not excluded by our studies either.

Myogenic contraction would not be expected from Bozler's categorization (8) of vascular smooth muscle as a multiunit (not spontaneously active) muscle, and is not in accord with Furchgott's observation (9) that in a bath of physiological salt solution most vascular smooth muscle has no spontaneous tone. However, these earlier conclusions were based on studies of vascular smooth muscle from large conduit vessels, which even in the present study did not show myogenic tone. A survey of the literature dealing with vascular myogenic tone has been presented in a previous publication (1).

It must also be recognized that in situ there may be an unidentified humoral agent (10) which may cause contraction of vascular smooth muscle and may also potentiate the response to neural and other humoral vascular smooth muscle activators. This material in the isolated bath causes contraction of all vascular smooth muscle. In the intact animal it may be responsible for non-neurogenic vascular tone. Intrinsic myogenic tone of those vessels that do have it.

The question of the quantitative contribution of the two determinants of non-neurogenic tone is unresolved. However, it is clear that a very important part of the total vascular bed is capable of developing a tonic contraction without extrinsic activation. Most vascular smooth muscle of resistance vessels possesses an intrinsic myogenic tendency to contract.

Acknowledgment

The authors are indebted to Dr. J. F. Villarreal of the Pharmacology Department of the University of Michigan for the rhesus monkeys used in this study and to Dr. Ruth McVaugh for her help in the preparation of the manuscript.

References

Myogenic Tone in Isolated Perfused Vessels: OCCURRENCE AMONG VASCULAR BEDS AND ALONG VASCULAR TREES

EIICHI UCHIDA and DAVID F. BOHR

Circ Res. 1969;25:549-555
doi: 10.1161/01.RES.25.5.549

Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1969 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7330. Online ISSN: 1524-4571

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/25/5/549