ROLE OF THE PERICYTES IN THE INNERVATION OF BLOOD CAPILLARIES

V. A. Shakhlamov

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The role of the pericytes in the motor innervation of the capillary wall is based on the following facts. 1) Contacts with nerve endings of the chemical synapse type are found on the body of the pericyte. 2) Each endothelial cell is in contact with the process of a pericyte, and at the points of contact between them nervous excitation is transmitted by the endothelial cells as in an electrical synapse. 3) Nervous impulses produce changes in the capillary lumen through alternation of swelling and collapse of the endothelial cells.

The pericyte is one of the least studied components of the capillary wall from both the structural and functional point of view, although it is now rightly assigned to the basal layer [7, 12]. The noncellular component of the basal layer, surrounding the pericyte on all sides, holds it firmly within the capillary walls. However, locating the pericyte within the basal layer does not explain its functions. The view that by contracting, it causes changes in the capillary lumen [12] has been rejected [15]. According to the author's observations, the pericyte has a role in the motor innervation of the blood capillaries.

Existence of a sympathetic innervation of the capillary wall has long been accepted by many investigators [2, 3, 5, 6, 10, 11, 13, 14]. From the writer's point of view the following observations are particularly important. 1) In response to stimulation of the sympathetic nerve trunk, contractions of the capillaries start in the nuclei of the Rougier cells, and "each Rougier cell is supplied by a sympathetic fiber" [13]. 2) During stimulation of the sympathetic nerve trunk, the change in lumen of the capillary is produced by swelling of the nuclei of the endothelial cells [19]. 3) Nervous structures [2], identified by the writer as terminal ramifications of centrifugal nerve fibers, have been demonstrated on capillary walls by silver impregnation methods. 4) Axo-angial synapses are found on the walls of blood vessels [1].

The authors cited above, because of the limitations imposed by light microscopy, were unable to detect structures concerned with the transmission of impulses from axon to capillary wall. Analysis of more recent investigations, using the electron microscope, has shown that none of these likewise sheds light on this problem. Admittedly, in a short annotation to an article on the contraction of endothelial cells under the influence of mediators of histamine type, Majno et al. [15], in 1969, noted that "individual pericytes are probably equipped with small nerve endings." However, as the text of this article and the photographs accompanying it show, there workers observed shapes similar to axons around the pericyte in the venule.

The results discussed in this communication represent observations made during experiments performed for other purposes and accumulated over a period of 8 years.

EXPERIMENTAL METHOD

The material consisted of capillaries from the human myocardium (biopsy material during transventricular commissurotomy), from the dog myocardium under normal conditions and during hypoxia, the rat myocardium during hypoxia and hyperoxia with normal and changed atmospheric pressure, and of the normal

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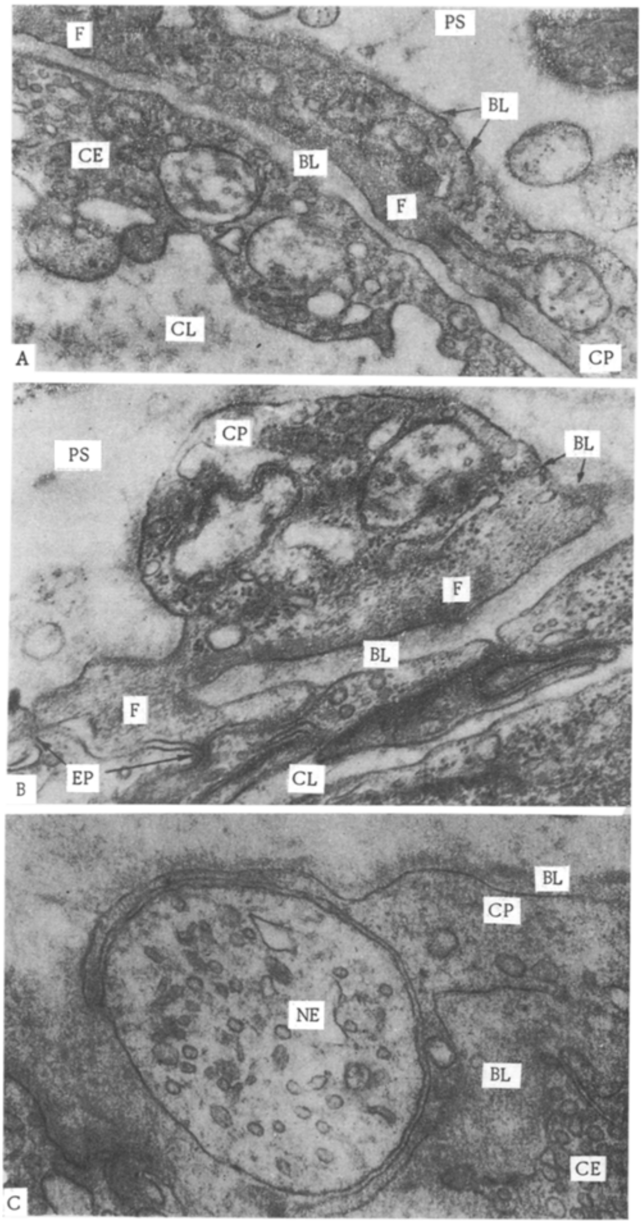

Fig. 1. Wall of a blood capillary from a dog's (A, B) and rat's (C) heart. CP) Cytoplasm of pericyte; CE) cytoplasm of endothelial cell; PS) pericapillary space; DL) adellular component of basal layer; EP) point of contact between membranes of pericyte and endothelial cell; F) fibrillary structures; NE) nerve ending; CL) capillary lumen. Magnification: a) 43,750 ×; B) 52,750 ×; C) 95,000 ×.

rabbit myocardium. Intravital observations also were made on capillaries of the mouse mesentry. Pieces of tissue for electron-microscopic examination were fixed by Palade's method and embedded in Araldite or a mixture of Araldite and Epon. Ultrathin sections were cut on the LKB ultratome, stained by Reynolds' method, and studied under the JEM-6C electron microscope with accelerating voltage 80 kV. To study the spatial relationships between the pericytes and neuronal structures, total preparations of two or three spinal ganglia from a chicken, stained with methylene blue in vivo by Milokhin's modification of Dogiel's method [4],* were studied under the light microscope.

EXPERIMENTAL RESULTS

In its ultrastructure the pericyte resembles both an endothelial and a smooth-muscle cell. Like the nucleus of the endothelial cell, the oval nucleus of the pericyte differs in its orientation relative to the long axis of the capillary, but the perikaryon of the pericyte often projects from the nucleus into the pericapillary space. The electron-optically translucent matrix of the cytoplasm, as well as the mitochondria and other organelles, are indistinguishable from those of the endothelial cells. The cytoplasm of the pericyte contains micropinocytotic vesicles (diameter 200-800 and 1000-1500 Å), located as a rule at the border of the cytoplasm facing the pericapillary space, although sometimes they are found at the border facing the endothelial layer of the capillary. The ATPase activity in the pericyte is revealed mainly in the membranes of the large vesicles (1000-1500 Å), whereas in the endothelial cells it is concentrated in the membranes of the micropinocytotic vesicles up to 800 Å in diameter [7-9]. The pericyte differs from the smooth-muscle cell both in the shape and in the orientation of the nucleus (in smooth-muscle cells the rod-shaped nucleus is perpendicular to the long axis of the vessel).

The pericyte characteristically possesses long cytoplasmic processes of complex shape, 0.04-0.35 μ in diameter, located perpendicularly to the long axis of the capillary, and sometimes the processes contain thin fibrils [7, 12] arranged along its long axis and often crossing from one process to another through the cytoplasm of the pericyte; where these fibrils exist, no other cell components are observed in the cytoplasm (Fig. 1A). Most processes, when passing through the noncellular component of the basal layer, approach the endothelial cells (Fig. 1B); the distance between the membranes of the endothelial cell and pericyte may reach 50-80 Å.

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*The specimens were prepared with the assistance of S. S. Reshetnikov, and advice on their interpretation was given by A. A. Milokhin (I. P. Pavlov Institute of Physiology, Academy of Sciences of the USSR).

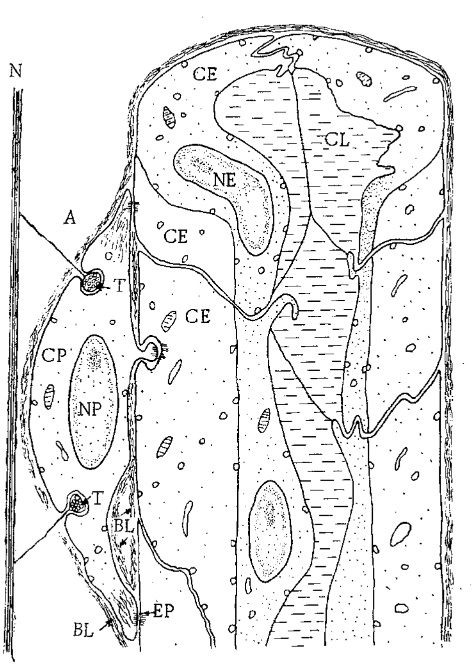

Fig. 2. Scheme of motor innervation of blood capillary wall: NE) nucleus of endothelial cell; NP) nucleus of pericyte; T) axon terminal; A) axon; N) nerve fiber. Remainder of legend as in Fig. 1.

Often the convex end of the pericyte process merges with the slightly concave surface of an endothelial cell, forming a macula occludens. In the zone of fusion, the membranes of the two cells are equally thick (70-80 Å).

Contact between the smooth-muscle and endothelial cells in the arterioles [16] differs from contact between the pericyte and endothelial cells in the capillaries: whereas in the arterioles the processes of the endothelial cells approach smooth-muscle cells, in the capillaries the situation is the opposite: processes of the pericyte approach the endothelial cell, and because of their length and great number, one pericyte may be in contact not with one, but with several endothelial cells. The writer has conclusively demonstrated that each endothelial cell forms a contact with the process of a pericyte. In total histological sections through the chicken spinal ganglion, terminals approaching the body of a pericyte were observed, and the nerve fibers from which they arose never gave branches into the connective tissue, even at the arteriolar level, so that these nerve fibers can be classed as effector preterminals [3-6].

Electron-microscopic investigation of the capillary wall revealed oval or circular structures, resembling axons on transverse section, in the immediate vicinity of the capillary and, in particular, of the pericyte. In addition, close contact was observed between the membranes of the pericytes and terminal part of the axon (Fig. 1C). Where such contacts took place, the acellular component of the basal layer was interrupted. Often invagination of shapes surrounded by an elementary membrane into the cytoplasm of the pericyte could be observed. These structures had the same electron-translucent matrix of their cytoplasm and structure of their mitochondria as an axon, and they contained numerous vesicles of varied diameter (200-800 Å), granular at the periphery, and either electron-optically translucent or with a dense center. These vesicles were very similar to synaptic vesicles in their ultrastructure. The distance between the membranes of the pericyte and the invaginated shapes described above was 100-240 Å.

On the basis of the available facts, the following scheme of the motor innervation of the blood capillaries can be postulated (Fig. 2). Endings of sympathetic nerve axons, approaching a pericyte, surrounded by the acellular component of the basal layer, perforated and become invaginated into the body of the pericyte, forming a snyapse-like contact with its plasmalemma, with vesicles in the presynaptic axoplasm resembling typical synaptic vesicles, and sometimes with specialized pre- and postsynaptic thickenings of the membrane. As many as 1 to 3 of these contacts may be present on the same pericyte. These synapses can be called axo-angial (after Dolgo-Saburov). It is clear from the ultrastructural properties of this contact that contact between the pericyte and nerve ending is most likely to be that of a chemical synapse (as described by de Robertis et al. [18]). The distance between the membranes of the pericyte and the ending of the axon is about 200 Å, so that it cannot prevent chemical transmission of the impulse [17]. It can be postulated that impulses are transformed in the cytoplasm of the pericyte (in some manner as yet unknown), and are transmitted through the processes of the pericyte to an endothelial cell, possibly not without the participation of the fibrils so frequently observed in the cytoplasm of these processes. A special role in impulse transmission may belong to the maculae occludentes, which are known to possess low resistance [12, 18]. The nervous impulse, reaching the endothelial cell, depolarizes its plasmalemma, thus facilitating the loss or accumulation of fluid by the cell, in all probability by penetration through the micropores in the plasmalemma [7, 8]. Swollen endothelial cells, completely occluding the lumen of the capillary, could be observed in electron micrographs and on intravital observation [10]. In vivo, a few seconds after swelling of the endothelial cell, it could be seen to collapse. This periodicity, leading in the first case to constriction of the lumen of the capillary, and in the second case to its opening for the movement of blood, is physiologically justified and cannot take place without the participation of the nervous system.

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