A novel mechanism for regulation of retinal blood flow by lactate: gap junctions, hypoxia, and pericytes

Julian H. Lombard
Department of Physiology, Medical College of Wisconsin, Milwaukee, Wisconsin

PERICYTES are proposed to play an important role in blood flow regulation in some organs. For example, in the kidney, pericytes in the descending vasa recta are important in regulating the distribution of blood flow between the juxtamedullary cortex and the inner and outer medulla (6). The retina has a very high density of pericytes, and these cells appear to play an important role in the regulation of retinal blood flow as well (1, 4). As noted by Yamanishi and coworkers (9) in the introduction to their study in this issue of the American Journal of Physiology-Heart and Circulatory Physiology, the low density of retinal microvessels, which is crucial to allow passage of light, introduces problems in regulating blood flow and oxygen delivery to the cells. This occurs because the volume of blood flow in the retinal capillaries is relatively low, despite the high flow velocity in individual vessels (4). This leads to a relatively large arteriovenous O2 difference and makes the retina particularly vulnerable to reduced perfusion and other conditions that could lead to decreased tissue PO2 (4). Pericytes may be involved in a number of vascular abnormalities that occur in the retina with different diseases, such as hypertension, diabetes, and glaucoma (1). In the latter case, pericytes may become less responsive to the local metabolic needs of the tissue, resulting in a diminished autoregulatory capacity, which eventually causes the optic nerve circulation to become vulnerable to the effects of increased intraocular pressure, leading to glaucomatous optic nerve damage (1).

The mechanisms regulating intracellular Ca2+ concentration ([Ca2+]i) and membrane potential in pericytes are every bit as complex as those regulating [Ca2+]i in arteriolar smooth muscle cells. For example, in the descending vasa recta of the kidney, K+ channels (2, 7, 11), voltage-activated Na+ channels (12), voltage-gated Ca2+ channels (11), chloride channels (10), Na+/H+ exchanger regulatory factor (5), and transient receptor potential channels (5) have all been suggested to play a role in the control of pericyte [Ca2+]i, and contractile state.

The study by Yamanishi et al. (9) utilizes time-lapse photography, perforated patch-clamp techniques (to measure ionic currents in retinal pericytes), and fura-2 to measure [Ca2+]i in pericytes of isolated rat retinal microvessels during exposure to lactate, a likely candidate for a metabolic regulator of blood flow in this tissue. Arteriolar diameters were also measured during exposure to lactate. Measurements were made in the presence and absence of different inhibitors and anoxia to identify specific mechanisms regulating pericyte [Ca2+]i, and contractile state. The authors (9) found that exposure of isolated retinal capillaries to lactate caused an increase in pericyte [Ca2+]i, leading to contraction of the pericytes and narrowing of the capillary lumen, whereas lactate caused dilation of isolated arterioles. However, exposure of the vessels to gap junction uncouplers and severe hypoxia or anoxia (equilibration with 100% N2), which also leads to gap junction uncoupling, changed the response of the retinal capillaries from contraction to relaxation.

There is substantial evidence that responses propagated through gap junctions between cells in the vascular wall coordinate the response of the microcirculation to vasodilator stimuli during normal blood flow regulation in skeletal muscle and other tissues (3, 8). These responses are coordinated via cell-to-cell junctions and involve changes in membrane potential and [Ca2+]i in the endothelial and smooth muscle cells (3). The study of Yamanishi et al. (9) reveals a potential role for gap junctions in regulating microcirculatory responses to changes in O2 availability in the retina as well. On the basis of their observations that gap junction uncouplers and hypoxia convert the lactate-induced constriction of retinal pericytes to a vasodilator response, the authors (9) propose the novel hypothesis that exposure of the retina to low levels of PO2 raises lactate levels and, in conjunction with hypoxia-induced gap junction uncoupling, leads to increased retinal blood flow under conditions of reduced PO2. In contrast, during normoxic conditions, normal levels of lactate released from well-oxygenated cells in the retina would act to reduce perfusion of capillaries in the immediate area, causing blood flow to be shunted away from areas that are adequately oxygenated. This proposed role of gap junctions in regulating the ultimate response of pericytes to lactate is an attractive and novel hypothesis that should provide valuable insight into the complex and important problem of blood flow regulation in the retina.

Another appealing aspect of the study (9) is the authors’ careful and systematic approach to dissecting specific membrane mechanisms that may participate in the regulation of [Ca2+]i in these cells. Yamanishi et al. (9) propose that the increase in [Ca2+]i that leads to contraction of the pericytes during exposure to lactate is mediated via a cascade of events that results in inhibition of Na+/Ca2+ exchangers (NCX) and pericyte-mediated constriction of the capillaries. These events include the importation of protons and lactate by monocarboxylate transporters and the secondary efflux of protons in exchange for Na+ via the Na+/H+ exchanger. The authors propose that this exchange of H+ for Na+ not only causes activation of the Na+/K+ pump (which modulates lactate-induced contraction of the pericytes but is not essential for the response) but also inhibits the NCX, which is the ultimate step leading to elevations in [Ca2+]i, and contraction of the pericytes. To account for the effects of gap junction uncouplers in their study, Yamanishi et al. (9) conclude that the NCX inhibited by lactate are located in the endothelial cells. Under these conditions, exposure to lactate would lead to elevations in [Ca2+]i in the pericytes when the gap junctions are intact but not during conditions of hypoxia, when gap junctions would be uncoupled. This careful and integrated experimental approach not only provides strong evidence for a novel mechanism
regulating pericyte $[\text{Ca}^{2+}]_i$ during exposure to lactate but would also be of value to graduate students seeking to increase their understanding of the role of various transport mechanisms in regulating membrane function and $[\text{Ca}^{2+}]_i$ in a highly specialized cell type.

NEW RESEARCH DIRECTIONS

Two important directions for future research regarding the role of pericytes in the regulation of retinal blood flow are to identify the mechanisms that operate to open and close the gap junctions in vivo and to define the Po$_2$ range over which gap junction uncoupling occurs. As noted by Yamanishi et al. (9), it is important to determine whether gap junction uncoupling occurs only during complete anoxia or whether gap junction uncoupling occurs at Po$_2$s that are more likely to be encountered in the retina when blood flow decreases, oxygen consumption increases, or hypoxemia is encountered. Demonstration of graded levels of gap junction uncoupling that correspond to the Po$_2$ range encountered in vivo would be a major step in establishing a role for pericytes in regulating retinal blood flow under physiological conditions.

REFERENCES


