Erythrocytes: Oxygen Sensors and Modulators of Vascular Tone

Through oxygen-dependent release of the vasodilator ATP, the mobile erythrocyte plays a fundamental role in matching microvascular oxygen supply with local tissue oxygen demand. Signal transduction within the erythrocyte and microves- sels as well as feedback mechanisms controlling ATP release have been described. Our understanding of the impact of this novel control mechanism will rely on the integration of in vivo experiments and computational models.

The matching of oxygen supply with oxygen demand in metabolically active tissue is a fundamental physiological process. Although a number of theories to explain this critical function have been proposed, none have been either universally accepted or fully tested in the intact microcirculation. Any attempt to comprehend the mechanism(s) by which oxygen delivery and metabolic need are matched must, by necessity, be based on the combination of experimental observations and theoretical models. In 1919, August Krogh, in conjunction with a mathematician colleague, K. Erlang, proposed the first oxygen trans- port model based on the assumption that each capi- lary is the sole supplier to a cylindrical region of tissue surrounding it (the Krogh cylinder) (55). Under this simple model, oxygen is assumed to diffuse in the radial direction with a uniform diffusivity and to be consumed in the tissue at a uniform constant rate. This model permitted Krogh to propose that capillary density must be actively regulated in response to changing metabolic activity to ensure adequate tissue oxygenation. Specifically, this model predicts that, in response to a fall in oxygen delivery, capillary density would increase to maintain tissue oxygenation. Specifically, this model predicts that, in response to a fall in oxygen delivery, capillary density would increase to maintain tissue oxygenation. However, for Krogh’s model to work, oxygen diffusion within the capillary must be able to keep up with oxygen consumption in nearby capillaries, resulting in an increase in their O2 saturation. Since O2 is transported by diffusion from arterioles to capillaries, it is also likely that O2 exchange occurs between capillaries with different O2 levels, as proposed in theoretical models (27, 37). This exchange would be consistent with quantitative studies of microvascular blood flow, which have demonstrated considerable spatial heterogeneity of capillary perfusion (93) and a corresponding hetero- geneity in O2 delivery. Thus groups of capillaries, rather than the single capillary on which Krogh’s model was based, need to be considered in evaluating the mechanisms responsible for maintaining tissue O2 requirements and uniform O2 delivery. As depicted in FIGURE 1B, the current view is that the microcircula- tion supplies oxygen to tissue using multiple vessel types that are functionally connected through both convective oxygen flow (blood flow) and diffusive oxygen transfer (23, 37). Inherent in this complexity is the need for a mechanism to direct the convective oxygen flow to regions of the tissue where oxygen is required to satisfy metabolic needs. This directed distribution of peripheral blood flow is analogous to the mecha- nisms inherent in the pulmonary circulation that direct blood flow to those regions of the lung that are well ventilated (96).

One might expect that mechanisms associated with blood flow regulation such as wall shear stress and pressure (myogenic tone) would be sufficient to prop- erly distribute blood flow and, consequently, O2 sup- ply within the arteriolar tree. However, at the microvascular level, total blood flow may not accur- ately reflect local O2 supply. The convective distribu- tion of oxygen within the arteriolar tree is impacted by the diffusional loss of oxygen to nearby erythrocytes in microvesels. Most of the diffusional loss of oxygen in the arteriolar is from erythrocytes near the wall of the vessel, that is, at the edge of the cell free plasma layer. Thus these cells have a lower O2 saturation than those nearer the center of the vessel (9, 25). At vessel bifur- cations, this uneven distribution affects convective oxygen supply to a greater or lesser extent depending on the relative flow in the downstream branches. For example, if blood flow into a downstream branch is...
very low, only plasma and the erythrocytes with lower $O_2$ will be skimmed into this branch (Figure 2). As flow into the side branches increases as a result of downstream vasodilation, flow into that branch will be derived from a larger cross-sectional region of the lumen of the upstream vessel, allowing blood with higher hematocrit and erythrocytes with higher $O_2$ saturation to enter that branch. Thus an increase in $O_2$ demand in one region of tissue would induce a redistribution of erythrocytes ($O_2$ delivery) not solely described by the simple redistribution of blood flow. In light of these complexities, it becomes abundantly clear that the simplistic Krogh approach to oxygen delivery will not adequately explain the complex interactions apparent in the intact microvasculature. Therefore, a local control mechanism must exist that is capable of sensing $O_2$ need and adjusting flow within the small arterioles feeding the capillary network.

Numerous studies have focused on the blood vessels themselves or on discrete regions within the tissue as the sensor of $O_2$ requirements in a tissue (18, 23, 26, 27, 43, 49, 64, 72). However, the exquisite accuracy in matching $O_2$ supply with $O_2$ demand in skeletal muscle in vivo mandates a control system that is both more sensitive and responsive than those previously described. The system required must be able to sense localized need and to initiate an integrated response that results in appropriate increases in local oxygen supply. Could this controller be as simple as the erythrocyte itself?

A Case for the Erythrocyte as a 
Vascular Controller

Fundamental to any system that regulates the delivery of appropriate amounts of oxygen to meet changing tissue needs is the requirement that the need be detected, quantified, and subsequently coupled to a mechanism that will appropriately alter blood flow ($O_2$ delivery). Such a mechanism requires integration among tissue gas exchange, tissue metabolism, and vascular smooth muscle function. Moreover, the process must be regulated within a narrow range (45). The vascular endothelium participates in controlling vascular caliber (7, 32, 54, 94) and coordinating the response to local, diverse stimuli initiated within the tissue (13, 17, 44, 77, 78, 94). It would be reasonable to suggest that one or more components of the oxygen transport pathway communicate directly or indirectly with the endothelium to appropriately alter microvascular perfusion.

In 1983, Stein and Ellsworth suggested (88) that, in severe hypoxia, the oxygen content of the blood supplying the tissue was more important than its oxygen tension for the maintenance of oxygen supply in hamster skeletal muscle. Oxygen content (oxygen saturation), a reflection of the extent of binding of oxygen to hemoglobin within the erythrocyte, is related to oxygen tension by the characteristic oxyhemoglobin dissociation curve. Oxygen tension determines the diffusive transfer of oxygen from the erythrocyte to the tissue. Thus, if oxygen content rather than oxygen tension were the important factor in regulating oxygen delivery, then the erythrocyte itself would assume a central role in the process since it contains the only component of the oxygen transport pathway that is directly influenced by oxygen content, hemoglobin. The oxygen content of the erythrocyte as it traverses a tissue is directly linked to the level of oxygen utilization of that tissue (Figure 3). Therefore, if the erythrocyte itself were able to sense oxygen need and affect an alteration in vascular caliber leading to appropriate changes in blood flow, this property of the erythrocyte would provide an efficient means of matching oxygen delivery (blood flow) with metabolic need, eliminating the requirement for a diverse network of sensing sites throughout the vasculature. It is intriguing to think that the mobile erythrocyte, whose level of oxygen content at a particular point in a tissue is directly linked to the level of oxygen utilization by that tissue, could itself augment blood flow and oxygen delivery whenever and whenever the need might arise.

The establishment that the erythrocyte, the major supplier of oxygen, also functions as a sensor of oxygen requirement to local vascular bed must be a signal that directly influences the past several decades in research on signaling G proteins Gs (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70). In humans, these cells transduce an ATP-dependent response to extracellular signals, such as a drop in oxygen tension, and are confirmed in hamsters by Stein and Ellsworth (88) in his collaborative work on the role of erythrocytes in oxygen transport from Erythrocyte to Tissue (85), rats (50), rabbits (22, 25, 70).
Changes in the delivery of oxygen to tissues require a mechanism that directly links the stimulus to the release of ATP. Over the past several years, it has become clear that erythrocytes release ATP in response to the combined effects of hypoxia and hypercapnia (5). More recent studies have shown that exposure to reduced oxygen tension (~35 Torr) alone is sufficient to stimulate ATP release from erythrocytes of hamsters (24), rabbits (45), rats (50), and humans (84). Although these studies have examined ATP release in response to reductions in oxygen tension, Jagger et al. (50), demonstrated that ATP efflux was linearly related to hemoglobin oxygen saturation in ATP release was later confirmed in human studies by González-Alonso and his collaborators (38, 39, 75). If release of ATP from erythrocytes is directly linked to a physiological stimulus, such as a decrease in oxygen saturation, then there must be a signal transduction pathway in the erythrocyte connecting the stimulus to the release.

A Proposed Signal Transduction Pathway for ATP Release from Erythrocytes

Strong evidence exists supporting the controlled release of ATP from erythrocytes in response to both physiological and pharmacological stimuli. Physiologically, erythrocytes release ATP in response to mechanical deformation (82, 83, 86), as would be encountered when these cells traverse the microcirculation, as well as in response to exposure to reduced oxygen tension (5, 15, 22, 50, 70). In both cases, the amount of ATP released is dependent increases in cAMP and ATP release from erythrocytes (6, 68, 80). However, Olearczyk et al. demonstrated that the G protein that is activated when erythrocytes are exposed to deformation or reduced transmembrane conductance regulator (CPT1) (83). Studies have clearly shown that activation of Gs-coupled β-adrenergic receptors and prostacyclin (IP) receptors in erythrocytes results in concentration-dependent increases in cAMP and ATP release from erythrocytes (6, 68, 80).

Erythrocytes contain millimolar quantities of adenosine 5’ triphosphate (ATP) (65), which is produced primarily by membrane-bound glycolytic pathways. In 1992, Bregfeld and Forrester reported that human erythrocytes release ATP in response to the combined effects of hypoxia and hypercapnia (5). It would prove a source of circulating ATP if, in the event of hypoxia, erythrocyte ATP were released in the local vicinity of the tissue, such as a decrease in oxygen saturation, as it desaturates during a fall in oxygen levels, elicits the release of ATP. This conclusion was further supported by an observed inhibition of ATP release on exposure of the erythrocytes to carbon monoxide, which would prevent the conformational change of hemoglobin in response to a drop in oxygen tension (50). The importance of hemoglobin oxygen saturation in ATP release was later confirmed in human studies by González-Alonso and his collaborators (38, 39, 75). If release of ATP from erythrocytes is directly linked to a physiological stimulus, such as a decrease in oxygen saturation, then there must be a signal transduction pathway in the erythrocyte connecting the stimulus to the release.
Vascular Control by ATP

If we accept that ATP is released from erythrocytes in a controlled manner as they perfuse a region of tissue with a low SO2, then this ATP must initiate a conducted vasodilation that extends beyond the site of initiation for there to be an effective increase in vascular perfusion (O2 delivery) (56) (FIGURE 3). Using arterioles in the intact hamster cheek pouch retractor muscle, McCullough et al. (59) demonstrated a dose-dependent conducted vasodilator response to the intraluminal ATP, but not to ADP, ADP, or ATPase. When ATP is applied, it can interact with receptors on smooth muscle cells to cause vasodilation, which would typically cause a decrease in blood flow. However, when ATP is released from erythrocytes, it can interact with endothelial purinergic receptors, resulting in the production of mediators that initiate vasodilation. This vasodilation is conducted in a retrograde fashion, resulting in increased blood flow to areas of increased oxygen demand.

**FIGURE 3.** The entrance of erythrocytes into tissue regions with a high oxygen demand

The entrance of erythrocytes into tissue regions with a high oxygen demand results in diffusion of oxygen to the tissue and a decrease in the oxygen saturation (SO2) of the hemoglobin within erythrocytes in the microcirculation. This decrease in SO2 stimulates the release of ATP from the erythrocyte via activation of a signaling pathway (see text) with the amount released proportional to the decrease in SO2. The erythrocyte-derived ATP can then interact with endothelial purinergic receptors, resulting in the production of mediators that initiate vasodilation. This vasodilation is conducted in a retrograde fashion, resulting in increased blood flow (oxygen supply) to areas of increased oxygen demand. Gi, heterotrimeric G protein; ATP, adenosine triphosphate; cAMP, 3'5'-adenosine monophosphate; PKA, protein kinase A; CFTR, cystic fibrosis transmembrane conductance regulator; ?, an as yet unidentified conduit for ATP release; PR, purinergic receptors; +, stimulation; endo, endothelium; SMC, smooth muscle cell.
increase in oxygen tension. One possibility is that the capillary membrane of the arterioles in that initiate SMC, smooth muscle membrane in the hemoglobin oxygen supply; ?, an aspect of initiation of vasodilation, is of the same order of magnitude as would be predicted to be released from erythrocytes perfusing a microvessel within a hypoxic tissue region (24, 59). Dietrich et al. (15) later established that the time course for sensing of a low-oxygen environment, the release of ATP from erythrocytes, and a vasodilatory response is on the order of 580 ms, supporting the potential physiological importance of this control mechanism. In recent studies in which the oxygen tension on the surface of an intact muscle was lowered in a stepwise fashion using a computer-controlled gas flow chamber, the increases in flow that occurred within the capillary bed were consistent with a time course (21).

When ATP is released into the vascular lumen, it can interact with receptors present on the endothelium that can elicit both endothelium-dependent and smooth muscle cell-dependent vasoactive responses, which would be conducted along the vasculature (Figure 4). Endothelial cells possess purinergic receptors that, when activated, stimulate the synthesis and release of several vasodilators. These vasodilators include nitric oxide (NO) as well as products of arachidonic acid metabolism. Although the receptor activated and the mediator released may vary in different tissues, the receptors present in the cerebral circulation have been particularly well characterized.

In the cerebral circulation, ATP and its related breakdown products, including adenosine, are vasoactive mediators. Forrester et al. found that intraluminal ATP was a potent vasodilator in the baboon cerebral circulation (29) and that topically applied ATP dilated cat pial vessels at a much lower concentration than adenosine (30). These reports led to the hypothesis that ATP, or a closely related breakdown product rather than adenosine, is the vasoactive purine in the cerebral circulation (30). Although in the cerebral microcirculation ATP, ADP, and adenosine are all potent vasodilators (14, 53), only ATP and ADP consistently caused conducted vasomotor responses (14, 53). Since at equimolar concentrations ADP was slightly less potent in causing dilatory local and conducted responses (53) than ATP, it is likely that ATP may be the primary agonist. This corresponds with observations by Ikuechi and Nishizaki where, in brain artery endothelial cells, ATP caused stronger potassium currents than ADP, whereas AMP had no effect (48).

Numerous studies have attempted to link neuronal activation, local oxygen tension, and cerebral blood flow. Neuronal activation can lead to a small, but significant, drop in local oxygen tension, which is followed by an increase in local blood flow (2). This neuronal activation-induced decrease in oxygen tension could elicit ATP release from erythrocytes, resulting in an increase in blood flow. Indeed, ATP is released from erythrocytes perfusing isolated cerebral arterioles within fractions of a second after entering the hypoxic vessel (15). Although not all studies have detected the drop in oxygen tension associated with neuronal activation (79), there is increasing evidence suggesting that, in the brain, ATP released from erythrocytes could contribute to a rapid initial increase in blood flow in response to neuronal activity.

ATP released from erythrocytes is known to activate specific P2 purinergic receptors on the vascular endothelium. Although it is simpler to consider two distinct classes of these P2 receptors, P2X and P2Y, more recent evidence indicates that the mammalian P2X1 and P2Y receptors are actually families of receptors consisting of seven P2X receptors (P2X1–7) and eight P2Y receptors (P2Y1–14) (1, 34). Studies in cerebral microvessels have delineated the specific receptors present and the vasoactive response to their stimulation. In isolated nonpressurized pial arterioles, Lewis et al. concluded that P2Y2- and P2Y6-like receptors are responsible for the observed vessel constriction (57). In isolated and pressurized rat penetrating arterioles, Horisuchi et al. reported that ATP constricts the vessels transiently via smooth muscle P2Y1 receptor and dilates the vessels via endothelial P2Y2 (47). Similarly, You et al. found that, in larger size cerebral arterioles, dilation to intraluminal ATP results from P2Y1 receptor stimulation (98). These receptors were confirmed to exist on hamster skeletal muscle arterioles (unpublished observations).

Regardless of the receptor that is activated, ATP-induced vasodilation is the result of the synthesis and activity of endothelium-derived relaxing factors. In skeletal muscle, McCullah (59) and Collins (10) each observed that the conducted vasodilatation to intraluminal ATP was eliminated following administration of a NO synthase inhibitor implicating NO as an important vascular mediator in these vessels. In addition, in large cerebral arterioles, endothelial P2Y1-specific stimulation was shown to release NO as well as a non-NO, non-cyclooxygenase-dependent factor (97, 98). Similarly, it was reported that in cerebral arterioles, endothelial P2Y1-specific stimulation releases both NO and a non-NO, non-cyclooxygenase-dependent factor, whereas P2Y2-specific stimulation releases only the...
non-NO, non-cyclooxygenase-dependent factor (46), possibly a cytochrome P450 monoxygenase product such as epoxyeicosanoids (EETs) (16). EETs can activate calcium-sensitive potassium channels, resulting in hyperpolarization (8, 31). In brain artery endothelial cells, purines induced strong potassium currents with ATP > ADP > AMP (48). In cerebral arteries, the dilution of ATP was preceded by hyperpolarization, and the dilution to ATP depended on large conductance BKCa and intermediate conductance ICa channels (32). Although there is significant evidence to suggest that NO is a regulator of vascular perfusion, controversy remains as to its source and mechanism of action. In 1996, Stamler and colleagues (51) proposed that the erythrocyte was responsible for regulating O2 delivery to tissues. Erythrocytes express messenger RNA for heme oxygenase, converting nitrite to NO, and hence making it possible for deoxyhemoglobin acts as a nitrite reductase, converting nitrite to NO, and hence making it possible for the erythrocyte to vasodilate arterioles in response to low O2 (11, 36, 71). However, it is not clear how this mechanism has sufficient temporal resolution to account for the observed rapid changes in the distribution of perfusion in response to local decreases in O2 tension. Importantly, unlike erythrocyte-derived ATP, neither SNO nor nitrite have been shown to be associated with conducted vasodilation of upstream resistance vessels in an intact vascular bed. Therefore, although each of these mechanisms could play a role in the regulation of certain aspects of tissue perfusion, neither would appear to fulfill the role we propose for ATP: a paracrine signal that is in the possibility of other Gi α and Gq-, and s-coupled receptors, respectively; IP3, prostacyclin receptor; KCa2+, calcium-activated potassium channel; KIR, inward rectifying potassium channel; NO, nitric oxide; P2y, ligand-gated ion channel purinergic receptor; P2x, ligand-gated ion channel purinergic receptor; PLA2, cytosolic phospholipase A2; sGC, soluble guanylyl cyclase; SOC, store-operated calcium channel; GAP, gap junction.

In these studies, donor sperm release from rats was decreased as well as decreased. Alvarez et al. (49) proposed that ADP may inhibit ATP release. This hypothesis was tested in the present study, and it was shown that ADP can activate the complementary effects of ATP released from erythrocytes to act as a vasodilation in response to ATP release. ADP is a product of the ATPase reaction and has potential for further physiological implications.

Control of ATP Release In Vivo: Feedback Mechanisms

Although ATP can stimulate the synthesis and release of multiple endothelial-derived vasodilators, ATP-induced increases in NO are important in both the cerebral and skeletal muscle microcirculations. It is important to recognize that NO-synthase in endothelial cells diffuses not only to vascular smooth muscle but in the brain, cerebral and skeletal muscle microcirculations. It is also released into the periphery in the form of the bioactive compound, S-nitrosomethyl (SNX), which is reported to be a potent vasodilator, is carried by hemoglobin and released as the hemoglobin O2 saturation falls in response to local O2 demand. Although there is support for this hypothesis (58, 87), questions remain as to its role in physiological conditions (35, 36, 71, 74). Recent work from the laboratories of Gladwin and Patel has provided evidence that deoxyhemoglobin acts as a nitrite reductase, converting nitrite to NO, and hence making it possible for the erythrocyte to vasodilate arterioles in response to low O2 (11, 36, 71). However, it is not clear how this mechanism has sufficient temporal resolution to account for the observed rapid changes in the distribution of perfusion in response to local decreases in O2 tension. Importantly, unlike erythrocyte-derived ATP, neither SNO nor nitrite have been shown to be associated with conducted vasodilation of upstream resistance vessels in an intact vascular bed. Therefore, although each of these mechanisms could play a role in the regulation of certain aspects of tissue perfusion, neither would appear to fulfill the role we propose for ATP: a paracrine signal that is in the possibility of other Gi α and Gq-, and s-coupled receptors, respectively; IP3, prostacyclin receptor; KCa2+, calcium-activated potassium channel; KIR, inward rectifying potassium channel; NO, nitric oxide; P2y, ligand-gated ion channel purinergic receptor; P2x, ligand-gated ion channel purinergic receptor; PLA2, cytosolic phospholipase A2; sGC, soluble guanylyl cyclase; SOC, store-operated calcium channel; GAP, gap junction.

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In these studies, incubation of erythrocytes with the NO donor spermine NONOate results in inhibition of ATP release from rabbit and human erythrocytes exposed to decreased oxygen tension (67). It has also been proposed that ADP, the first degradation product of ATP, can inhibit ATP release from erythrocytes (95). Under this hypothesis, ATP released from the erythrocytes in response to physiological stimuli is metabolized by ecto-enzymes, resulting in the generation of ADP. ADP can then activate P2Y13 receptors present on erythrocytes resulting in decreases in intracellular cAMP and reduced ATP release (95). The finding that ATP release from erythrocytes is inhibited by the endothelium-derived vasodilator released from the endothelium in response to ATP (NO) as well as the first degradation product of that nucleoside (ADP) demonstrates the potential for negative feedback regulation of this physiologically important signaling pathway.

**Pathological Consequences of a Defect in this Control Mechanism**

Recently, it was reported that erythrocytes of humans with Type 2 diabetes (DM2), a condition in which cardiovascular disease accounts for nearly one-half of the original model of blood flow regulation (3). This later model is consistent with the hypothesis that regulation of microvascular oxygen delivery based on local wall shear rate (shear-dependent vasodilation) and blood pressure (myogenic factors). Krogh’s original model of oxygen supply assumed that increased oxygen delivery to tissue resulted from an increase in the number of perfused capillaries (“capillary recruitment”). However, in vivo experiments in skeletal muscle (20) indicate that most capillaries are perfused under resting conditions. As such, increased flow would result in a more uniform distribution of erythrocytes to already perfused capillaries rather than perfusion of additional capillaries.

Most of the above features have been included in theoretical models of diameter adaptation in microvascular networks (73) and more recently in a theoretical model of blood flow regulation (3). This latter model is consistent with the hypothesis that regulation of microvascular O2 delivery based on O2 saturation-dependent release of ATP by erythrocytes leading to conducted vasodilation can account for experimentally observed increases in perfusion in response to increased oxygen demand. This idealized model used a simulated network consisting of only seven representative segments and did not consider diffusive exchange of O2 between capillaries and arterioles. Therefore, it remains to be shown whether the features described above, including erythrocyte-derived ATP, when included in a more comprehensive model, can fully explain the O2-dependent microvascular flow regulation that occurs in vivo. In addition, other key issues that need to be addressed

"...the erythrocyte could be a novel target for the development of drugs for the treatment of vascular insufficiency."
include 1) whether there is a primary location within the network where the need for changes in O2 supply are sensed or controlled is exercised throughout the arteriolar tree to ensure proper distribution of O2 supply; 2) the inherent time scale of the regulatory system (i.e., how fast different sub-systems respond and what the limiting factors are); 3) the vessels in the network that are involved in the response to a given stimulus; and 4) the limitations of the system's ability to control local O2 delivery. Future progress toward understanding the role of erythrocyte-derived ATP in the regulation of O2 delivery within the microcirculation will depend on combining new in vitro experiments, detailed computational modeling, and model testing and validation using its in vivo counterparts under a range of physiological and pathophysiological conditions.

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REVIEWS


The heterogeneity of the ventricular and function of the cerebrospinal fluid (CSF) models has high relevance to understanding the relationship between CSF and brain health.