Hypoxic pulmonary vasoconstriction (HPV) is the rapid, reversible increase in pulmonary vascular resistance that occurs when the alveolar oxygen tension falls below a threshold level. In conditions characterized by segmental alveolar hypoxia (e.g., single-lung anesthesia, atelectasis, or pneumonia), HPV is restricted to the segments of the vasculature serving the hypoxic lobe, thereby achieving ventilation/perfusion matching and optimizing systemic PO2 without significantly elevating pulmonary artery (PA) pressure. During global hypoxia, as occurs in the normal fetus, or after birth, with ascent to altitude or hypoventilation syndromes, HPV is involved in the initiation and/or maintenance of pulmonary hypertension (PHT). HPV is found in virtually all mammals, although populations and species truly adapted to life at high altitude (Tibetan natives, yaks, etc.) have diminished or absent HPV, an adaptation that allows them to avoid PHT while living in their rarefied environment. The importance of understanding HPV extends beyond its role in pathophysiology; its mechanism has relevance to O2 sensing in other cardiovascular tissues, including the ductus arteriosus, the type 1 cell of the carotid body, the adrenomedullary cells, and the neuroepithelial body.

O2-sensing systems consist of a sensor that alters the production of a mediator in response to changes in PO2. The mediator, in turn, alters the function of one or more effectors, which ultimately mediate the physiological response of the system. Teleologically, it is optimal that the sensor monitors a variable that is rapidly modified by mild hypoxia before ATP levels decline or tissue damage occurs. O2-sensing systems maintain systemic PO2 within a tight physiological range and thus stabilize ATP production and promote survival during the periodic exposures to hypoxia that occur in most aerobic lives. Often the sensor, mediator, and effector are linked in a functional unit. This review will focus on the proposed sensing unit involved in HPV, in which the sensor is the proximal portion of the mitochondrial electron transport chain (ETC); the mediators are ETC-derived, activated O2 species (AOS); and the effectors are redox-sensitive, voltage-gated K+ channels (Kv channels). Although it is unlikely that there is a single, universal O2 sensor, there is evidence suggesting that the proximal mitochondrial ETC is involved in O2 sensing in several tissues and species. The potential contribution of a similar putative redox sensor, membrane-bound NADPH, will also be considered. In most of the O2-sensitive cardiovascular tissues, H2O2 or other AOS have been proposed as diffusible mediators. This brief review will deal with identifying the molecular mechanism of HPV, highlighting controversies where they exist. We apologize to the many authors whose work has helped shape our understanding of HPV but who were not cited because of space constraints, and we also acknowledge that other theories for the mechanism of HPV exist.

Properties of HPV

There are certain cardinal features of HPV that must be accounted for by any proposed mechanism.

HPV is intrinsic to resistance PAs. HPV occurs in isolated lungs, small PA rings, and even in isolated PA smooth muscle cells (SMCs; Fig. 1). Although most segments of the pulmonary circulation, including pulmonary veins, constrict in response to hypoxia, proximal PAs dilate (3).

HPV onsets and resolves rapidly. HPV onsets within 1 min of exposure to hypoxia, is sustained during hypoxia, and rapidly reverses on return to normoxia (Fig. 1A).

HPV is triggered by hypoxia, not anoxia. Because of the unique location of resistance PAs, near the terminal airways and alveoli, they preferentially respond to alveolar rather than intravascular PO2. In humans, HPV onsets with inspired O2 concentrations ≥ 12%. In vivo, HPV is uniphasic, a plateau pressure being attained within minutes that is not increased by repeated challenges or altered when hypoxic ventilation is sus-
tained for hours. This is also true in isolated lungs perfused with blood; however, HPV increases with repeated challenges when Krebs-albumin perfusate is used.

Although HPV is modulated by numerous mediators, its core mechanism is independent of endothelial and neurohumoral factors. Although the core mechanism of HPV is postulated to reside within PA SMCs, the magnitude of HPV is modulated by circulating mediators and the autonomic nervous system. HPV is diminished by inhibitors of the endothelin, leukotriene, or serotonin pathways and is enhanced by inhibitors of prostaglandin or nitric oxide synthesis. To date, it seems that none of these mediators is essential to HPV (for review, see Ref. 8).

Dependence on extracellular Ca$^{2+}$. HPV is inhibited by antagonists (Fig. 1C) and enhanced by agonists of the voltage-dependent, L-type Ca$^{2+}$ channel (e.g., BAY K 8644; for review, see Ref. 8). Although this suggests that HPV is dependent on the influx of extracellular Ca$^{2+}$, there is debate as to the relative contribution of release of intracellular Ca$^{2+}$ vs. Ca$^{2+}$ influx through the L-type Ca$^{2+}$ channel. However, most of the reports suggesting a major role for Ca$^{2+}$ release derive from studies of isolated arteries in which pretreatment with a vasoconstrictor, which might itself trigger release of Ca$^{2+}$, has been used to "prime" HPV.

Hypoxia inhibits whole cell K$^+$ current in PA but not systemic arterial SMCs. Interestingly, hypoxia dilates systemic arteries (Fig. 1A) and either increases or fails to inhibit K$^+$ current (I$\text{K}$) in systemic arterial SMCs (for review, see Ref. 8). However, 4-aminopyridine (4-AP) inhibits I$\text{K}$ in SMC from both PA and renal arteries. The opposing hypoxic responses of the PA vs. systemic arteries may result either from tissue-specific differences in the O$_2$ sensor or in the response of the K$^+$ channels to a common redox mediator.

O$_2$-sensitive Kv channels: the effector mechanism of HPV

HPV is initiated, at least in part, by the inhibition of a family of O$_2$-sensitive Kv channels leading to membrane depolarization, opening of the L-type Ca$^{2+}$ channel, and vasoconstriction (Fig. 1, A–C). The activity of the L-type Ca$^{2+}$ channel is largely regulated by membrane potential (E$\text{M}$), which is established by K$^+$ channels. The more K$^+$ inhibition occurs, the more depolarized the PA SMC, and the more opening of the L-type channels (a pathway leading to influx of extracellular Ca$^{2+}$). As predicted by this hypothesis (Fig. 1G), Ca$^{2+}$ channel blockers substantially reduce HPV (Fig. 1C), whereas Kv channel inhibitors, such as 4-AP, cause pulmonary vasoconstriction. Inhibitors of

FIGURE 1. Conservation of K$^+$ channels in the mechanism of O$_2$ sensing. A: representative trace showing that hypoxia simultaneously constricts the pulmonary and dilates the renal circulation. An isolated lung and kidney were perfused in series with blood-free perfusate, containing inhibitors of nitric oxide (NO) and prostaglandin synthesis, at a constant flow rate. Hypoxia (P$_{\text{O2}}$ ~40 mmHg) was induced by ventilating the lungs with a hypoxic gas. PAP, pulmonary arterial pressure. B: whole cell patch-clamp experiments show that hypoxia inhibits K$^+$ currents (I$\text{K}$) and depolarizes pulmonary artery (PA) smooth muscle cells (SMCs) from resistance PAs. E$\text{M}$, membrane potential. Reproduced from Ref. 3, with permission. C: Ca$^{2+}$ channel blocker verapamil inhibits hypoxic pulmonary vasoconstriction (HPV), suggesting that hypoxic depolarization of PA SMCs leads to vasoconstriction by activating L-type Ca$^{2+}$ channels. Reproduced from Ref. 13, with permission. D–F: hypoxia rapidly and reversibly inhibits I$\text{K}$ in other O$_2$-sensitive cells [neuroepithelial bodies (D), carotid bodies (E), and PC-12 cells (F)]. Reproduced with permission from Refs. 9, 12, and 20, respectively. G: proposed mechanism for HPV, featuring the effector portion of the pathway.
the large-conductance Ca\(^{2+}\)-sensitive K\(^+\) channel (BK\(_{Ca}\)) and ATP-sensitive K\(^+\) channels (K\(_{ATP}\)) do not increase normoxic pulmonary vascular resistance in adult mammals, suggesting that these channel types do not control basal PA tone. The electrophysiology of the PA SMC parallels the hemodynamics of the pulmonary circulation, in that PA SMCs from resistance PAs depolarize in response to 4-AP but not in response to BK\(_{Ca}\) or K\(_{ATP}\) blockers (reviewed in Ref. 8).

There has recently been significant progress in establishing the molecular identity of the O\(_2\)-sensitive K\(^+\) channels involved in HPV. This task is difficult because the I\(_{K}\) is an ensemble of current conducted through many channel types. However, comparing the pharmacology of the O\(_2\)-sensitive K\(^+\) current (I\(_{KvO2}\)) with that of clonal K\(^+\) channels in expression systems has been useful in suggesting candidate O\(_2\)-sensitive channels. I\(_{KvO2}\) in PA SMCs is slowly inactivating, 4-AP sensitive, and resistant to charybdotoxin (8). This profile tends to exclude a role for 4-AP-insensitive channels (i.e., BK\(_{Ca}\)), rapidly inactivating channels (e.g., Kv1.4 and Kv4.3), and charybdotoxin-sensitive channels (e.g., homotetrameric Kv1.2 and Kv1.6 channels). Furthermore, Kv1.2 homotetramers have a current morphology (slowly activating with run-up on repeat stimulation) quite distinct from that seen in PA SMCs and are exquisitely sensitive to charybdotoxin, suggesting that the role of Kv1.2 in HPV is most likely through its involvement in charybdotoxin-insensitive heterotetramers with Kv1.5 (for review, see Ref. 8). Kv2.1, alone or in combination with Kv9.2 \(\alpha\)-subunits, also has a pharmacological profile and O\(_2\) sensitivity consistent with a role in HPV.

Several groups have proposed that multiple Kv channels are involved in HPV, including homo- and heterotetramers comprised of Kv1.2, Kv1.5, Kv2.1, and Kv3.1b (for review, see Ref. 8). To identify which of the clonal Kv channels accounts for HPV, we developed an immunoelectropharmacological approach to identifying the channels involved in creating the O\(_2\)-sensitive I\(_{K}\) mosaic. This approach utilized the specificity of anti-Kv channel antibodies to functionally inhibit Kv current in PA SMCs from resistance PAs. Introduction of anti-Kv2.1 or anti-Kv1.5 (but not anti-inward rectifier K\(^+\) channel antibodies) via the patch pipette technique inhibits a portion of I\(_{K}\) and partially depolarizes E\(_{m}\) (reviewed in Ref. 7). Kv1.5 is an appealing candidate for involvement in HPV because it is 4-AP sensitive and charybdotoxin insensitive. Furthermore, in rodents exposed to chronic hypoxia, acute HPV is selectively suppressed, whereas response to other vasoconstrictors is preserved. Loss of acute HPV persists for several days after return to normoxia and is associated with decreased Kv1.5 expression in cultured PA SMCs (18) and in vivo (data from our laboratory show reduced Kv1.5 and Kv2.1). Kv1.5 expression is also reduced in other forms of PHT. In addition, anorexigens, such as dexfenfluramine, that cause vasoconstriction and outbursts of PHT inhibit I\(_{K}\) (others have shown that they directly block both Kv1.5 and Kv2.1). Because pharmacological and immunologic probes lack the specificity to distinguish the contribution of candidate channels to I\(_{K}\), we examined the effect of targeted deletion of Kv1.5 in mice. The Kv1.5 knockout mouse displays reduced HPV (Fig. 2) and a loss of I\(_{Kv1.5}\). Hypoxia- and 4-AP-sensitive component of I\(_{K}\) (4). There is some residual HPV in Kv1.5 knockout mice and some O\(_2\)-sensitive Kv current in their PA SMCs, perhaps reflecting contributions of other types of K\(^+\) channels.

### Oxygen sensors: the redox theory of HPV

The redox hypothesis explains the pulmonary vascular sensor in electrical terms. The flow of electrons down a redox sequence can lead to changes in membrane potential, which can in turn modulate ion channels and affect smooth muscle tone. This hypothesis integrates the role of mitochondrial respiration in determining pulmonary vascular tone. In conditions of hypoxia, the reduction of oxygen leads to an increase in the redox potential, which in turn activates oxygen-sensitive channels such as Kv1.5, leading to reduced HPV. This physiological mechanism provides a link between metabolic state and vascular reactivity.

![FIGURE 2. HPV is reduced in mice lacking voltage-gated K\(^+\) channel Kv1.5. Schematic shows the effects of selective deletion of Kv1.5 \(\alpha\)-subunits in mouse PA SMCs. Representative traces show impaired HPV in 4th division PA rings from Kv1.5 knockout (\(+/+) vs. wild-type (+/+) mice. A subtraction of current densities in wild-type vs. Kv1.5 knockout PA SMCs reveals that wild-type mice have an O\(_2\)-sensitive outward current (I\(_{Kv1.5}\)).](http://physiologyonline.physiology.org/)
cascade (the mitochondrial ETC) that accompanies normal metabolism creates a small flux of signaling molecules (AOS). Both AOS generation and ETC function occur in proportion to PO2. These AOS can exit the mitochondria and alter the reduction/oxidation status of specific, sulfhydryl-rich amino acids in key enzymes and proteins (notably K+ channels). Reduction or oxidation can thus alter channel function and link PO2 to vascular tone.

Redox potential is a measure of the relative tendency of a substance to acquire or donate electrons. In the case of mitochondrial ETC, electrons flow from electron donors, NADH and FADH, to distal electron recipients because of the dinucleotide's more negative reduction-oxidation potential. The more negative this potential, the more likely a substance is to donate an electron. In the mitochondrial ETC, electrons flow down a potential gradient of redox potential ranging from $-0.35$ for NADH/NAD$^+$ to $+0.82$ for O$_2$/H$_2$O. Physiological generation of AOS occurs during normal electron shuttling by cytochromes within the ETC. Although most of the O$_2$ used by the mitochondrial ETC is eventually reduced to H$_2$O, ~2% is incompletely reduced, due to single electron reductions, and yields AOS, particularly the superoxide radical.

AOS were originally thought to be too toxic to serve a physiological role, but like nitric oxide, in low amounts these species are important signaling molecules. Although AOS can be produced by xanthine oxidase, cyclooxygenase, and nitric oxide synthase, the PO2-responsive production of AOS primarily occurs in the mitochondrial ETC and several vascular oxidases, including NAD(P)H and novel vascular oxidases (NOX). Both the mitochondrial ETC and vascular oxidases generate the superoxide radical. Superoxide radical is very unstable, and its short diffusion radius makes it a poor signaling molecule; however, it is rapidly converted to the more stable and diffusible H$_2$O$_2$ by Mn superoxide dismutase (SOD) in the mitochondria and Cu/Zn SOD in the cytoplasm. H$_2$O$_2$ production is thereby still linked to PO2 and is an attractive mediator.

AOS can regulate the function of target proteins by donating electrons to highly negatively charged residues. Reduction or oxidation of the sulfhydryl groups of amino acids, such as cysteine or methionine, may cause conformational changes in the K+ channel that change channel gating and open probability. A number of other important signaling substances such as kinases and phosphatases are now also known to be redox sensitive. Therefore, AOS, whether diffusing out of mitochondria or produced by membrane-bound oxidases, can affect target proteins that control vascular tone, including K+ channels.

![FIGURE 3](http://physiologyonline.physiology.org/) The proximal mitochondrial electron transport chain (ETC), but not gp91phox subunit-containing NADPH oxidase, is involved in HPV. A-C: mice lacking the gp91phox subunit (gp91−/−) and wild-type mice (gp91+/+) have similar hypoxia-sensitive I_K and HPV compared with wild-type mice, even though gp91−/− lungs have greatly decreased chemiluminescence (CL). All, angiotensin II. Reproduced from Ref. 5, with permission. D: tone and activated O2 species (AOS) production were studied simultaneously in isolated perfused rat lungs. Hypoxia and rotenone (10 μM) have concordant effects on tone (rapid constriction), and both decrease lung AOS production, measured by using lucigenin-enhanced (Luci) CL. Rotenone, like hypoxia, inhibits I_K in PA SMCs. Reproduced from Ref. 15, with permission.
can serve as physiological signals, rather than mediators of toxic injury, was controversial when it was initially proposed (1) and perhaps still is. Under conditions of alveolar hypoxia, production of AOS falls in proportion to the inspired O2 concentration (FiO2). The PA SMCs respond to the withdrawal of the tonic oxidant signal with redox inhibition of K+ channels (Fig. 4).

The data supporting this “redox hypothesis” can be summarized briefly as follows. First, AOS are formed in the lung and PAs in proportion to the ambient PO2. Second, inhibitors of the proximal mitochondrial ETC, such as rotenone and antimycin A, mimic hypoxia. Both hypoxia and mitochondrial ETC inhibitors reduce the production of AOS in the lung, inhibit Kv current, and elicit pulmonary vasoconstriction (Fig. 3D) (2). Furthermore, unlike other drug classes, including distal ETC inhibitors, proximal ETC inhibitors (such as rotenone and antimycin A) cause PA constriction (2), carotid body activation, and the relaxation of systemic arteries and the ductus arteriosus (unpublished data; see Ref. 8 for review). Although it is tempting to explain hypoxia and metabolic inhibitor-induced pulmonary vasoconstriction on the basis of the ability of these stimuli to eventually cause ATP depletion, Buescher et al. (see Ref. 8) used nuclear magnetic resonance spectroscopy to show that ATP is preserved in isolated lungs during moderate hypoxia. Teleologically, the role of the lung as a net supplier, rather than a consumer, of O2 (in marked contrast to all other organs) may explain the unique occurrence of hypoxia-induced vasoconstriction in PAs (unpublished data; see Ref. 8 for review).

Mitochondria as O2 sensors. Inhibitors of the mitochondrial ETC mimic hypoxia’s effects on the carotid body (e.g., increase

**FIGURE 4.** Proposed redox theory of HPV. The redox theory suggests that AOS are produced in proportion to PO2 by O2 sensors, likely complexes I and III of the mitochondrial ETC, and possibly also cytochrome-based vascular oxidases. The changes in AOS production alter the gating and open probability of the effector of HPV, the O2- and redox-sensitive Kv channels, such as Kv1.5 and Kv2.1.
sinus nerve activity) and PA (cause vasoconstriction; Fig. 3). Both hypoxia and mitochondrial ETC inhibitors reduce the production of AOS in the lung, inhibit a Kᵥ current (2), and elicit pulmonary vasoconstriction (Fig. 3D). As early as 1986, a link was proposed between mitochondrial AOS production, cellular redox status, K⁺ currents, and HPV (1). Subsequently, it was confirmed that inhibitors of complex I and III, but not complex IV, cause pulmonary vasconstriction, inhibit Iᵥ and prevent further HPV, suggesting the existence of a mitochondrial O₂ sensor (2). The mitochondria generate a superoxide anion at complexes I and III that is dismutated by mitochondrial-specific MnSOD, generating the diffusible signaling molecule H₂O₂. Recently, another group (19) has offered supportive evidence for the role of mitochondria, with findings indicating that mitochondria complex III is important in HPV. They showed that proximal ETC blockers suppressed HPV without affecting the response to other vasoconstrictors. Their conclusions, implicating the proximal ETC in oxygen sensing, are in agreement with our hypothesis. However, they found that AOS were increased by hypoxia and ETC inhibition, whereas others found that, in the pulmonary circulation, hypoxia decreases AOS (5, 10, 14). This discrepancy may relate to the fluorescent probe they used to measure AOS, which is sensitive to nitric oxide and can itself generate AOS (see below). Inhibition of ETC function not only decreases the production of AOS but also shifts the ratio of cytosolic redox couples, such as NADH/NAD and GSH/GSSG, to a more reduced ratio (15). This “backup” of reduced substances in the cytosol occurs rapidly and at a physiologically relevant range of Po₂ (15). Thus when mitochondrial electron shuttling is diminished by hypoxia, there is both less AOS production and an accumulation of the reduced form of several electron donors in the cytosol. Either or both of these interrelated redox changes could also serve an O₂ sensor function.

**NADPH oxidase.** NADPH oxidase, another putative source of signaling AOS for HPV, is a flavocytochrome present in phagocytes, carotid body type 1 cells, neuroepithelial bodies, PA SMCs, and endothelial cells. It includes a membrane-bound flavocytochrome containing two subunits, gp91phox and p22phox, and the cytosolic proteins p47phox and p67phox, which bind to the flavocytochrome to form the active enzyme complex (Fig. 3, A–C, and Fig. 4) (5). The NADPH oxidase uses both flavin and heme groups to shuttle electrons from NADPH to oxygen, yielding superoxide radical. NADPH oxidase produces AOS in proportion to Po₂ and has been touted as a possible redox O₂ sensor (14). Both NADPH and NADH oxidase, named according to their substrate preference, are present in PA SMCs. AOS formation by the NADH isoform decreases as Po₂ falls and is inhibited by diphenyleneiodonium (DPI; see Ref. 8 for review). These are features consistent with the oxidase acting as a redox O₂ sensor. Although DPI inhibits Iᵥ, it causes minimal vasoconstriction and inhibits HPV (see Ref. 8 for review). However, the lack of a greater constrictor effect may be because DPI is also a L-type Ca²⁺ channel blocker (see Ref. 8 for review). Unfortunately, DPI nonspecifically inhibits flavoprotein-containing enzymes, including NADPH oxidases, nitric oxide synthase, and complex I of the mitochondrial ETC (see Ref. 8 for review). Thus DPI is a poor tool for assessing the physiologic role of NADPH oxidase in regulating vascular tone. The development of mice deficient in NADPH oxidase activity due to mutation of the X-linked gene for gp91phox provided an opportunity to study the role of NADPH oxidase in HPV. Most O₂-responsive cell types contain a similar form of the oxidase, containing the gp91phox component. HPV is preserved in mice lacking a functional gp91phox despite a marked reduction in AOS production in their lungs (Fig. 3, A–C) (5). This suggests that NADPH oxidases containing gp91phox are not required for HPV (5). Moreover, rotenone constriction is enhanced in these mice, consistent with the mitochondrial O₂ sensor hypothesis (5). Preserved O₂ sensing has also been reported in the type 1 cell of the carotid body from gp91phox knockout mice, although the O₂ sensing is impaired in their neuroepithelial bodies.

**Controversies**

**Controversies related to models and experimental methodologies.** Many of the controversies in the field relate to the usage of models that do not display the fundamental characteristics of HPV. Another cause of confusion is the substitution of anoxia or chemical hypoxia (e.g., induced by dithionite) for authentic hypoxia. Unfortunately, papers using these suboptimal models or hypoxia surrogates often refer to the phenomenon studied as “HPV” and the stimulus as “hypoxia” over looking the intrinsic dissimilarities between the model and HPV in vivo. For example, proximal PAs dilate to hypoxia and after a brief constriction anoxia causes pulmonary vasodilation; finally, dithionite does not elicit HPV in vivo. Another cause for diversity in findings among laboratories studying HPV is the failure to uniformly adhere to the tight pH and temperature standards when studying HPV. HPV is largely absent at room temperature and is diminished by severe alkalosis. Finally, models that only display HPV when primed should be viewed with caution; priming is not required in vivo or in isolated lungs. An even more insidious cause of confusion is failure to define whether one is studying one of the myriad pathways that modulate the magnitude of HPV or its core mechanism.

**Controversies regarding the molecular identity of the redox sensor.** Vascular SMCs contain gp91phox homologs, called NOX, which also preferentially use NADPH as a substrate. NOXs are inhibited by DPI and are important sources of AOS in systemic vascular SMCs (11). However, most studies of NOX have been performed in systemic arteries and have measured AOS production in response to vasoconstrictors (e.g., angiotensin II) or mitogens (e.g., platelet-derived growth factor). There is little evidence that NOX are involved AOS pro-
duction in PA SMC. It is noteworthy that angiotensin II does not cause an acute change in AOS production in mouse lungs at doses that cause vasoconstriction (5). Perhaps the predominant source of AOS differs between PAs, in which AOS may be signaling molecules serving to optimize O₂ uptake from the environment, vs. systemic arteries, in which AOS may be involved in the pathogenesis of atherosclerosis (which is rare in PAs).

Effects of hypoxia and ETC inhibitors on PA SMC AOS production. There is debate as to whether hypoxia and ETC inhibitors decrease (2, 5) or increase (19) production of AOS. As discussed in the section on mitochondrial O₂ sensors, much of the controversy results from the use of 2',7'-dichlorodihydrofluorescein diacetate (DCF), an agent that preferentially detects nitric oxide (as mentioned in the product insert) and that can itself increase generation of one of the species it is used to detect, namely H₂O₂ (16). Rota et al. (16) studied DCF by using several techniques, including electron spin resonance, and concluded that “DCF cannot be used conclusively to measure superoxide or hydrogen peroxide formation in cells undergoing oxidative stress.”

Controversy regarding endothelin and the mechanism of HPV. In rats, the endothelin (ET)α-receptor antagonist BQ-123, but not the ETβ-receptor antagonist BQ-788, inhibits HPV. However, the K⁺ATP antagonist glibenclamide prevents BQ-123 inhibition of HPV. Thus ET-1 reinforces HPV by suppressing compensatory, vasodilator K⁺ATP channel activity (17) and also can inhibit Kv current via a protein kinase C-dependent mechanism. Although endothelin’s role in HPV remains unclear, it may be an important mechanism in reinforcing the hypoxic response.

Conclusion

We propose the following model for O₂ sensing. In normoxia, the proximal mitochondrial ETC produces AOS, some of which (such as H₂O₂) can diffuse to the plasmalemma, oxidizing and thus opening K⁺ channels. This favors normoxic membrane hyperpolarization and vasodilatation. Hypoxia is sensed in the proximal ETC, and perhaps vascular oxidases, resulting in a decrease in AOS production. Decrease in AOS levels and the associated increases in reducing equivalents in the cytoplasm promote a reduced state that causes K⁺ channel inhibition, membrane depolarization, and vasoconstriction.

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