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MINIREVIEW

Altered Pulmonary Vasoreactivity in the Chronically Hypoxic Lung

L. A. SHIMODA, J. S. K. SHAM, J. T. SYLVESTER

Division of Pulmonary and Critical Care Medicine, Johns Hopkins University, School of Medicine Baltimore, Maryland, USA

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Summary

Prolonged exposure to alveolar hypoxia induces physiological changes in the pulmonary vasculature that result in the development of pulmonary hypertension. A hallmark of hypoxic pulmonary hypertension is an increase in vasomotor tone. *In vivo*, pulmonary arterial smooth muscle cell contraction is influenced by vasoconstrictor and vasodilator factors secreted from the endothelium, lung parenchyma and in the circulation. During chronic hypoxia, production of vasoconstrictors such as endothelin-1and angiotensin II is enhanced locally in the lung, while synthesis of vasodilators may be reduced. Altered reactivity to these vasoactive agonists is another physiological consequence of chronic exposure to hypoxia. Enhanced contraction in response to endothelin-1 and angiotensin II, as well as depressed vasodilation in response to endothelium-derived vasodilators, has been documented in models of hypoxic pulmonary hypertension. Chronic hypoxia may also have direct effects on pulmonary vascular smooth muscle cells, modulating receptor population, ion channel activity or signal transduction pathways. Following prolonged hypoxic exposure, pulmonary vascular smooth muscle exhibits alterations in K^+ current, membrane depolarization, elevation in resting cytosolic calcium and changes in signal transduction pathways. These changes in the electrophysiological parameters of pulmonary vascular smooth muscle cells are likely associated with an increase in basal tone. Thus, hypoxia-induced modifications in pulmonary arterial myocyte function, changes in synthesis of vasoactive factors and altered vasoresponsiveness to these agents may shift the environment in the lung to one of contraction instead of relaxation, resulting in increased pulmonary vascular resistance and elevated pulmonary arterial pressure.

Key words

Contraction • Endothelin-1 • Angiotensin II • Nitric oxide • Membrane potential • Pulmonary hypertension

Evidence of Active Vasoconstriction during Chronic Hypoxia

Long-term exposure to alveolar hypoxia is associated with luminal narrowing of the pulmonary vasculature and, consequently, elevated pulmonary arterial pressure. The reduction in vascular caliber is not only due to structural remodeling of the pulmonary vasculature, but also due to sustained active vasoconstriction of pulmonary arterial smooth muscle.

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Fax+4202 24920590
E-mail: physres@biomed.cas.cz
http://www.lf2.cuni.cz/physiolres/physiolres.htm

Active contraction of vascular smooth muscle during chronic alveolar hypoxia is evidenced by an acute reduction in pulmonary arterial pressure (P_{Pa}) in response to inhaled oxygen therapy or vasodilatory agents (Jones and Evans 1997, MacNee *et al.* 1983, Mionard *et al.* 1994, Oka *et al.* 1993).

In rats, exposure to simulated high-altitude (17 000 ft) for 3-4 weeks caused significant right ventricular hypertrophy indicated by an increase in the ratio of right ventricle to left ventricle plus septum weights from 0.32 in low altitude rats to 0.58 in the chronically hypoxic rats (Oka *et al.* 1993) and increased mean P_{Pa} from ~19 mm Hg to 41 mm Hg. Administration of a K^+ channel agonist reduced mean P_{Pa} by 22%, compared to a 15% reduction in mean P_{Pa} observed in rats breathing 80 ppm nitric oxide (NO) (Oka *et al.* 1993). In patients with chronic obstructive lung disease (COPD), which is often characterized by chronic hypoxia, intravenous infusion of acetylcholine, an endothelium-dependent vasodilator, rapidly reduced mean P_{Pa} from 31 to 28 mm Hg (Adnot *et al.* 1993). Inhalation of NO (40 ppm) decreased P_{Pa} in a concentration-dependent fashion, reaching an 18 % reduction in mean P_{Pa}, within 2-3 min after the beginning of inhalation, with no associated change in cardiac output (Adnot *et al.* 1993). Consistent with these findings, later studies reported similar reductions in mean P_{Pa} during inhaled NO therapy (Jones and Evans 1997, Mionard *et al.* 1994). Acute reductions in mean P_{Pa} by 10-30 % (ranging from ~25mm Hg to ~20mm Hg) have been noted in COPD patients after increasing FIO_2 to 100 %, although the decrease in P_{Pa} under these conditions was likely due, in part, to a fall in cardiac output (Jones and Evans 1997, Mionard *et al.* 1994).

Mechanisms of Active Vasoconstriction

The mechanisms underlying pulmonary vasoconstriction in response to chronic hypoxia and subsequent development of pulmonary hypertension are incompletely understood; however, a number of possible mechanisms have been proposed. *In vivo*, pulmonary arterial smooth muscle cell (PASMC) tone is influenced by vasoconstrictor and vasodilator factors secreted from the endothelium, lung parenchyma and in the circulation. Attenuated endothelium-dependent relaxation, depressed contraction in response to acute hypoxic challenge and enhanced contraction to endothelin-1 (ET-1), serotonin (5-HT), angiotensin II (ANG II) and histamine have been described in chronic hypoxic pulmonary hypertension models (McMurtry *et al.* 1978, Porcelli and Bergman 1983, Rodman *et al.* 1990, Wanstall and O'Donnell 1990, Rui and Cai 1991, Eddahibi *et al.* 1991, 1992, Carville *et al.* 1993, MacLean *et al.* 1995). Altered reactivity to pharmacological agonists is a physiological consequence of chronic exposure to hypoxia that, combined with changes in synthesis, may contribute to the active contraction of pulmonary vascular smooth muscle by shifting the environment to one of contraction instead of relaxation, resulting in increased pulmonary vascular resistance and elevated pulmonary arterial pressure. Chronic hypoxia may also have direct effects on pulmonary vascular smooth muscle cells, modulating receptor populations, ion channel activity or signal transduction pathways.

Vasodilators

The vascular endothelium secretes vasodilators such as NO and prostacylin (PGI_2). Under normal conditions, inhibition of NO or PGI_2 production sometimes (Cremona *et al.* 1999, Ferrario *et al.* 1996, Gordon *et al.* 1993, Nelin and Dawson 1993, Walker *et al.* 1982), but not always (Archer *et al.* 1989, Nishiwaki *et al.* 1992, Weir *et al.* 1976), caused constriction in the lung, suggesting a possible role for endogenous vasodilators in maintenance of basal tone in the pulmonary circulation. Under conditions where tone was elevated, such as during hypoxia, inhibition of NO and PGI_2 synthesis potentiated vasoconstriction (Weir *et al.* 1976, Archer *et al.* 1989), implying that these vasodilators act to oppose vasoconstriction in the presence of increased tone. Impairment in the action or synthesis of these vasodilators during hypoxic exposure could, therefore, contribute to the development of hypoxic pulmonary hypertension. Consistent with this notion, mice deficient in the endothelial, or constitutive, form of nitric oxide synthase (eNOS), the enzyme responsible for NO production, exhibited exaggerated development of chronic hypoxic pulmonary hypertension (Steudel *et al.* 1998). Vasorelaxation of pulmonary arteries to agents that induce NO secretion, such as acetylcholine and bradykinin, was attenuated in models of chronic hypoxic pulmonary hypertension (Rodman *et al.* 1990, Adnot *et al.* 1991, Rui and Cai 1991, Carville *et al.* 1993, Dinh-Xuan *et al.* 1993, Eddahibi *et al.* 1992). The diminished relaxation in response to agonists that cause vasodilation by release of NO could be due to decreased endothelial cell capacity to produce NO

following prolonged hypoxic exposure; however, conflicting results have been shown regarding the effect of hypoxia on the expression and activity of eNOS. Evidence has been presented for both upregulation (Shaul *et al.* 1995, Le Cras *et al.* 1996, Xue and Johns 1996, Resta *et al.* 1997) and downregulation (Kourembanas *et al.* 1997, Fike *et al.* 1998) of eNOS during chronic hypoxia. These results suggest that other mechanisms in addition to decreased NOS, such as reduced availability of cofactors, may be responsible for diminished NO production during hypoxia. PGI_2 production was also decreased by hypoxia in pulmonary arterial endothelial cells from neonatal calves (Badesch *et al.* 1989) as well as in endothelial cells exposed to hypoxia *in vitro* (Kourembanas *et al.* 1997).

Reports of blunted pulmonary vascular responses to endothelium-dependent vasodilators may be due to alterations in signal transduction pathways in smooth muscle rather than decreased production of vasodilator factors. For example, cyclic GMP pathways were impaired in pulmonary vascular smooth muscle of some chronically hypoxic animals (Crawley *et al.* 1992, Rodman *et al.* 1990, Rui and Cai 1991). However, inhalation of NO gas resulted in pulmonary vasodilation and reduction of pulmonary artery pressure in patients with hypoxic pulmonary hypertension (Horstman *et al.* 1998, Mionard *et al.* 1994). Similarly, in animal models of chronic hypoxia, administration of either exogenous NO or PGI_2 caused selective vasodilation of hypoxic pulmonary vasoconstriction (Russell *et al.* 1993, Kouyoumdjian *et al.* 1994, Roos *et al.* 1996). These findings suggest that NO signal transduction pathways were intact following prolonged exposure to hypoxia.

Similar to NO, carbon monoxide (CO) is a gaseous vasodilator that increases smooth muscle cGMP levels and inhibits hypoxic induction of the vascular endothelial growth factor (VEGF), ET-1 and platelet-derived growth factor (PDGF)-β genes (Morita and Kourembanas 1995, Liu *et al.* 1998). In pulmonary vascular smooth muscle, the enzyme heme-oxygenase (HO) catalyzes the breakdown of heme to CO, iron and biliverdin (Morita *et al.* 1995). Three isoforms of HO have been identified: HO-1 is the inducible form of the enzyme, HO-2 is the constitutively expressed isoform and HO-3 appears to be a neuronal isoform. Hypoxia increased the transcriptional rate of the HO-1 gene, resulting in elevated CO levels (Kourembanas *et al.* 1993, Morita *et al.* 1995) and transgenic mice deficient in the HO-1 gene exhibited greater right ventricular hypertrophy, suggesting potentiation of hypoxic pulmonary hypertension (Yet *et al.* 1999). These findings suggest that HO-1, and possibly its product CO, may play a physiologic role in modulating the development of chronic hypoxic pulmonary hypertension.

Vasoconstrictors

Numerous studies have demonstrated that the chronically hypoxic pulmonary vasculature exhibits increased vasoreactivity in response to ET-1, 5-HT, ANG II, noradrenaline and histamine (Porcelli and Bergman 1983, Wanstall and O'Donnell 1990, Eddahibi *et al.* 1991, MacLean *et al.* 1995). Endothelin-1, a 21-amino acid peptide secreted by the vascular endothelium, has both vasoconstrictive and mitogenic properties (Lippton *et al.* 1989, Wanstall and O'Donnell 1990, Horgan *et al.* 1991, Peacock *et al.* 1992, Bonvallet *et al.* 1993, Zamora *et al.* 1993, Barman and Pauly 1995, Shimoda *et al.* 1997, 1998), and is believed to play a significant role in the development of active vasoconstriction during chronic hypoxic pulmonary hypertension (Bonvallet *et al.* 1994, Chen *et al.* 1995, DiCarlo *et al.* 1995, Eddahibi *et al.* 1995, Oparil *et al.* 1995). At concentrations between 10^{-11} and 10^{-7} M, ET-1 constricted isolated pulmonary arteries (Wanstall and O'Donnell 1990, Horgan *et al.* 1991, Bonvallet *et al.* 1993, Barman and Pauly 1995, MacLean *et al.* 1995, McCulloch *et al.* 1998, Shimoda *et al.* 1997, 1998) and caused long-lasting increases in vascular resistance in isolated perfused lungs (Lippton *et al.* 1989) through activation of endothelin-A (ET_A) receptors on pulmonary vascular smooth muscle. In the presence of preconstricting agents, ET-1 caused vasodilation at low doses through activation of endothelin-B (ET_B) receptors on the endothelium and subsequent release of NO and PGI_2 (de Nucci *et al.* 1988). ET-1 mRNA, protein and circulating plasma levels were markedly increased during prolonged hypoxia in animal models (Chen *et al.* 1995, DiCarlo *et al.* 1995, Elton *et al.* 1992) and in patients with chronic obstructive pulmonary disease (Ferri *et al.* 1995, Stewart *et al.* 1991). The elevation in ET-1 levels correlated with increased pulmonary artery pressure (Stewart *et al.* 1991, Ferri *et al.* 1995). The mechanism by which ET-1 levels were elevated in response to hypoxia remains elusive, although the promoter of the ET-1 gene contains a consensus site for hypoxia-inducible factor 1 (HIF-1) binding, and hypoxic regulation of this gene by HIF-1 has been demonstrated in systemic endothelium (Hu *et al.* 1998). Expression of lung ET_A and ET_B receptors was increased during hypoxia (Li *et al.* 1994), although ET-1-induced vasodilation was impaired (Eddahibi *et al.* 1991, 1993),

consistent with alterations in receptor density and distribution in the pulmonary vasculature (McCulloch *et al.* 1998). The alterations in ET-1 secretion and ET receptor distribution during chronic hypoxia may act in concert to increase ET-1-induced constriction.

Similar to ET-1, ANG II is both a vasoconstrictor and pulmonary fibroblast and smooth muscle cell mitogen (Morrell *et al.* 1998, Nguyen *et al.* 1994). Circulating angiotensin I is converted to its active form, ANG II, by angiotensin converting enzyme (ACE) located on vascular endothelium. Lung ACE activity and, consequently ANG II production, was reduced during exposure to hypoxia (Kay *et al.* 1985, Oparil *et al.* 1988), yet acute administration of ACE inhibitors reduced pulmonary artery pressure and pulmonary vascular resistance in COPD patients (Bertoli *et al.* 1986, Peacock and Matthews 1992) and in animal models of chronic hypoxia (Morrell *et al.* 1995b, Nong *et al.* 1996, van Suylen *et al.* 1998). The discrepancy between ACE activity/ANG II secretion and administration of ACE inhibitors may be explained in that ACE activity was selectively increased in small resistance arteries of lungs exposed to chronic hypoxia (Morrell *et al.* 1995a), and that these localized changes may not have been accurately reflected in measurements of whole lung ACE activity or ANG II production. In addition to vasoconstrictive properties, ANG II upregulated ET_A receptor expression on pulmonary vascular smooth muscle (Hatakeyama *et al.* 1994), while ET-1 augmented ACE activity (Kawaguchi *et al.* 1991) and ANG II secretion (Kawaguchi *et al.* 1990) in pulmonary arterial endothelium. These studies indicate a link between the renin-angiotensin and endothelin systems in pulmonary remodeling during chronic hypoxia.

Alterations in Pulmonary Arterial Smooth Muscle Cell Function

Abnormalities in pulmonary vascular smooth muscle are also likely to contribute to the alterations in vasoreactivity during chronic hypoxic pulmonary hypertension. Intracellular Ca^{2+} concentration is a primary factor regulating vascular tone. Through the control of Ca^{2+} influx and cytosolic Ca^{2+} concentration ($[Ca^{2+}]_i$), membrane potential may play a vital role in regulating vascular caliber. Agents that cause vasoconstriction, including both ET-1 and ANG II, caused elevations in $[Ca^{2+}]_i$, while vasorelaxation, as occurs in response to NO and PGI_2, was accompanied by a reduction in $[Ca^{2+}]_i$ (Cornfield *et al.* 1993, Bakhramov *et al.* 1996, Guibert *et al.* 1996, Yuan *et al.* 1996, Shimoda *et al.* 2000). In the absence of external stimuli, however, inhibition of K^+ channels and depolarization may contribute to the development of pulmonary hypertension by increasing cytosolic Ca^{2+} concentration.

Pulmonary arterial smooth muscle cells from animals exposed to chronic hypoxia exhibited membrane depolarization (Suzuki and Twarog 1982, Smirnov *et al.* 1994, Shimoda *et al.* 1999a) and attenuation of voltage-gated K^+ (K_V) current (Smirnov *et al.* 1994, Shimoda *et al.* 1999a), which may be the result of reduced expression of K_V channel α subunit proteins (Wang *et al.* 1997). Furthermore, Ca^{2+}-activated K^+ (K_{Ca}) channel activity was reduced in pulmonary artery smooth muscle cells (PASMCs) cultured under hypoxic conditions (Peng *et al.* 1997). Inhibition of K^+ channels by hypoxia may explain why agonists that cause relaxation by activating K^+ channels were more effective in pulmonary arteries from chronically hypoxic animals (Rodman 1992). In PASMCs, resting membrane potential appears to be regulated predominantly by specific subtypes of voltage-gated K^+ (K_V) channels, which are 4-aminopyridine (4-AP)-sensitive and charybdotoxin (ChTX)-insensitive since 4-AP, but not ChTX, caused membrane depolarization and increased $[Ca^{2+}]_i$ (Yuan 1995, Archer *et al.* 1996, Shimoda *et al.* 1998). Consequently, the reduction in K_V current observed following prolonged hypoxia may contribute to the observed depolarization.

Both acute hypoxic vasoconstriction and *in vitro* smooth muscle proliferation were associated with a rise in $[Ca^{2+}]_i$ (Cornfield *et al.* 1993, 1994, Harder *et al.* 1985, Madden *et al.* 1985) and were prevented by voltage-gated L-type Ca^{2+} channel antagonists (McMurtry *et al.* 1976, Kruse *et al.* 1994). Since pulmonary smooth muscle cells from chronically hypoxic animals are depolarized, it has been speculated that an increase in $[Ca^{2+}]_i$ due to activation of voltage-gated Ca^{2+} channels is the mechanism underlying chronic hypoxic pulmonary hypertension. This speculation is contradicted, however, by data indicating that voltage-gated Ca^{2+} channel antagonists did not prevent development of hypertension secondary to chronic hypoxia (Johnson *et al.* 1986, Michael *et al.* 1986, Oka *et al.* 1993). Furthermore, acute administration of vasodilators (MacNee *et al.* 1983, Michael *et al.* 1986, Jin *et al.* 1989, Jones and Evans 1997), but not voltage-gated Ca^{2+} channel antagonists (Brown *et al.* 1983, Johnson *et al.* 1986, Singh *et al.* 1985), reduced pulmonary artery pressure in patients with COPD. Recent findings also indicate that although resting

$[Ca^{2+}]_i$ is elevated in PASMCs from chronically hypoxic rats to levels twice greater than those observed in PASMCs from normoxic animals, L-type Ca^{2+} channel antagonists were not effective in reducing $[Ca^{2+}]_i$ in these cells (Shimoda *et al.* 1999b). These findings indicate that activation of other Ca^{2+} regulatory pathways such as nonselective cation channels, Na^+/Ca^{2+} exchange or ATP-dependent plasmalemmal Ca^{2+} pumps may be affected by chronic exposure to hypoxia, and suggest possible areas for future investigation.

It is unclear whether the changes observed in chronically hypoxic pulmonary vascular smooth muscle were due to alterations in a single subtype of pulmonary arterial smooth muscle cells or reflect the growth of a new phenotype. Hypoxia stimulates smooth muscle cell growth both *in vivo*, as evidenced by medial thickening in small pulmonary arterioles during prolonged hypoxia, as well as in cell culture systems (Rabinovitch *et al.* 1979, Hales *et al.* 1983, Meyrick and Perkett 1989, Kourembanas *et al.* 1993, Chen *et al.* 1995, Quinn *et al.* 1998). It has been suggested that the vascular wall is comprised of at least four subtypes of pulmonary arterial smooth muscle cells (Frid *et al.* 1994), which may have different electrophysiological profiles (Archer *et al.* 1996), and that hypoxia induced the growth of specific phenotypes (Dempsey *et al.* 1997, Frid *et al.* 1997). Further experimentation is required to delineate the etiology of the functional changes induced by hypoxia in pulmonary vascular smooth muscle.

Numerous agonists, including both ET-1 and ANG II cause contraction, in part, by inhibition of K_V channels (Salter *et al.* 1998, Shimoda *et al.* 1998). Under conditions of chronic hypoxia, the ability of ET-1 to inhibit K_V current is lost (Shimoda *et al.* 1999a). Consistent with this finding, the ability of ET-1 to cause depolarization was also absent in PASMCs from chronically hypoxic rats (Shimoda *et al.* 1999a). In contrast, the ability of ANG II to inhibit K_V channels was enhanced following prolonged hypoxia (Shimoda *et al.* 1999b). While the enhanced effect of ANG II on K_V channels could explain, in part, the enhanced reactivity to this agonist, the increased contraction in response to ET-1 appears to occur despite a reduction in this part of the signal transduction pathway. ET-1 has also been demonstrated to inhibit K_{Ca} channels (Peng *et al.* 1998). Inhibition of K_{Ca} channels by ET-1 increased in PASMCs cultured under hypoxic conditions (Peng *et al.* 1997). However, in other studies, ET-1 was demonstrated to either have no effect on or stimulate K_{Ca} channels (Salter *et al.* 1998, Shimoda *et al.* 1999a), with enhanced stimulation of K_{Ca} channels following *in vivo* exposure to hypoxia (Shimoda *et al.* 1999a).

Application of ET-1, ANG II and 5-HT to PASMCs was accompanied by an increase in intracellular Ca^{2+} concentrations $[Ca^{2+}]_i$ (Bakhramov *et al.* 1996, Guibert *et al.* 1996, Sugawara *et al.* 1996, Yuan *et al.* 1997, Hyvelin *et al.* 1998, Shimoda *et al.* 2000). The effect of chronic hypoxia on the ability of ANG II and 5-HT to increase $[Ca^{2+}]_i$ has not been studied. With respect to ET-1, the increase in $[Ca^{2+}]_i$ was markedly reduced following prolonged exposure to hypoxia (Shimoda *et al.* 1999b). Under normoxic conditions, ET-1 increased $[Ca^{2+}]_i$ via both Ca^{2+} influx and release (Bakhramov *et al.* 1996, Sugawara *et al.* 1996, Hyvelin *et al.* 1998, Shimoda *et al.* 2000). The small rise in $[Ca^{2+}]_i$ observed in response to ET-1 in PASMCs from chronically hypoxic rats was abolished in the presence of nifedipine or following removal of extracellular Ca^{2+} (Shimoda *et al.* 1999b). These results suggest that the ET-1-induced $[Ca^{2+}]_i$ increase in PASMCs from chronically hypoxic rats was entirely dependent on Ca^{2+} influx through voltage-gated Ca^{2+} channels, and that mechanisms activating Ca^{2+} release from intracellular stores in response to ET-1 are no longer operative in these cells. Interestingly, the ET-1-induced activation of voltage-gated Ca^{2+} channels in PASMCs from chronically hypoxic rats did not appear to result from depolarization, since ET-1 had no effect on membrane potential in these cells (Shimoda *et al.* 1999b). The activation of the voltage-gated Ca^{2+} channels by ET-1 may instead be due to the ability of ET-1 to increase open probability of Ca^{2+} channels independent of membrane potential as, at a given holding potential, Ca^{2+} current in coronary arterial smooth muscle cells was markedly enhanced in the presence of ET-1 (Goto *et al.* 1989). Since membrane potential in PASMCs from chronically hypoxic rats was significantly depolarized, to a range where voltage-gated Ca^{2+} channels may be activated, application of ET-1 may be able to induce Ca^{2+} influx through these channels in the absence of a change in membrane potential.

In pulmonary arterial smooth muscle from normoxic rats, blockade of voltage-gated Ca^{2+} channels significantly reduced maximum tension induced by ET-1 (Horgan *et al.* 1991, Barman *et al.* 1995, Shimoda *et al.* 1998). In contrast, maximum tension generated in pulmonary vascular smooth muscle from chronically hypoxic animals in response to ET-1 was only slightly reduced by voltage-gated Ca^{2+} channel antagonists (Shimoda *et al.* 1999b). These findings suggest that following chronic exposure to hypoxia, ET-1 caused contraction in the pulmonary vasculature via mechanisms largely independent of $[Ca^{2+}]_i$ changes since the ET-1-induced increase in $[Ca^{2+}]_i$ was completely prevented after blockade of voltage-gated Ca^{2+} channels. ET-1 can

increase the Ca^{2+}-sensitivity of the contractile apparatus, resulting in contraction that is independent of $[Ca^{2+}]_i$ (Goto *et al.* 1989, Nishimura *et al.* 1992). The signal transduction pathways responsible for ET-1-induced Ca^{2+}-independent contraction are currently unknown, but may involve protein kinase C-dependent activation of mitogen-activated protein kinase (MAPK) (Horowitz *et al.* 1996), which phosphorylates the thin filament-associated contractile regulatory protein, calponin (Menice *et al.* 1997). Unphosphorylated calponin binds to actin, inhibiting myosin MgATPase; phosphorylation of calponin causes its release from the actin filament and allows cycling of cross bridges and development of tension (Winder and Walsh 1990). ET-1 has also been shown to induce phosphorylation of calponin (Menice *et al.* 1997), lending support to this theory. Other investigators have proposed mechanisms involving activation of myosin light chain kinase or inactivation of myosin light chain phosphatase (Adam *et al.* 1990, Abe *et al.* 1991, Nishimura *et al.* 1992).

Conclusions

Pulmonary hypertension, whether due to active contraction or structural remodeling, is the major pathophysiologic characteristic of chronic hypoxia. The pathogenesis of chronic hypoxic pulmonary vasoconstriction is complex, and includes decreased production of vasodilating factors, increased production of vasoconstrictors and alterations in smooth muscle cell phenotype. Following prolonged hypoxic exposure, pulmonary vascular smooth muscle exhibits alterations in K^+ current, membrane depolarization, elevation in resting $[Ca^{2+}]_i$ and changes in signal transduction pathways. Although the etiology of these smooth muscle cell alterations remains poorly understood, the changes that occur in response to prolonged hypoxia clearly amplify the effects of the predominately vasoconstrictive factors released by the endothelium. It is presently unclear whether the reduction in NO and PGI_2 production is a primary event or a consequence of endothelial cell dysfunction. The roles of ET-1 and ANG II in the development of hypoxic pulmonary vasoconstriction remain the areas of great interest. The vasoconstrictive properties of these agonists, their induction by hypoxia, and the ability of both ET-1 and ANG II to modulate the production of other vasoactive agents make them strong candidates as mediators of this disease process. Future data detailing the effects of prolonged hypoxia on ET-1 and ANG II signal transduction should allow the development of pharmacological therapies targeted at preventing the deleterious effects of these vasoconstrictors and provide effective means of treatment and prevention of chronic hypoxic pulmonary vasoconstriction.

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Reprint requests

Larissa A. Shimoda, Ph.D., Division of Pulmonary and Critical Care Medicine, 5501 Hopkins Bayview Circle, Baltimore, MD 21224, USA, FAX (410)-550-2612, E-mail: shimodal@welch.jhu.edu