ENDOTHELINS AT HIGH ALTITUDE

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Introduction

First discovered in 1988 by Yanagisawa and colleagues in Japan, endothelin-1 is a potent vasoactive peptide generated by the vascular endothelium. Endothelin-1 plays an important role in the regulation of blood pressure and vascular tone in humans and is implicated in the pathogenesis of a number of cardiovascular diseases. A rise in pulmonary artery pressure is a key feature of human acclimatisation to high altitude. Failure to adjust to high altitude is associated with profound pulmonary hypertension and the development of the life-threatening condition, high altitude pulmonary oedema (HAPE). Recent attention has focused on the role of endothelin-1 in the development of HAPE. Targeting the endothelin system may offer a new opportunity to develop a novel and more selective approach to the treatment of this potentially fatal condition.

The Endothelins

The endothelins (1, 2 and 3) are a family of three isopeptides. Endothelin-1, the most potent vasoconstrictor, is the only family member produced by endothelial cells and is known to play an important role in the regulation of human vascular tone and blood pressure *in vivo* (Haynes and Webb, 1994)(Haynes et al, 1996).
Endothelin-1 is produced and secreted de novo by the endothelium both basally and in response to various stimuli. Generation of endothelin-1 is regulated at the transcriptional level and culminates in the proteolytic cleavage of its precursor, a 38 amino acid peptide, big endothelin-1, by a specific endothelin converting enzyme, to produce the mature, active, 21 amino acid peptide. Humoral agents, inflammatory mediators, shear stress and hypoxia are all known to stimulate endothelin-1 production *in vitro* (Emori et al, 1991)(Haynes and Webb, 1993). Rats exposed to hypoxia have raised plasma concentrations of endothelin-1 that correlate inversely with arterial pO_2 (Horio et al, 1991). Nitric oxide, a potent vasodilator *in vivo*, inhibits the production of endothelin-1 (Boulanger et al, 1990).

The actions of endothelin-1 on vascular tone are mediated by two receptors. The ET_A receptor is found abundantly on vascular smooth muscle and mediates potent vasoconstriction (Arai et al, 1990). ET_B receptors are present predominantly on endothelial cells (Sakurai et al, 1990) and are responsible for endothelin-1 mediated vasodilatation, mainly through an increase in nitric oxide and prostanoid generation (De Nucci et al, 1988)(Tsukhara et al, 1994). In addition, ET_B receptors have also been described on the vascular smooth muscle (Davenport et al, 1993) and may produce vasoconstriction in certain situations. However, recent studies in the forearms of healthy subjects suggest the predominant action mediated by the ET_B receptor is endothelial-dependent vasodilatation (Verhaar et al, 1998).

Clearance of endothelin-1 has been demonstrated in the lungs, liver and kidneys (De Nucci et al, 1988)(Fukuroda et al, 1994)(Dupuis et al, 1996). Although a specific clearance mechanism has not been identified, the ET_B receptor is clearly implicated

(Fukuroda et al, 1994).

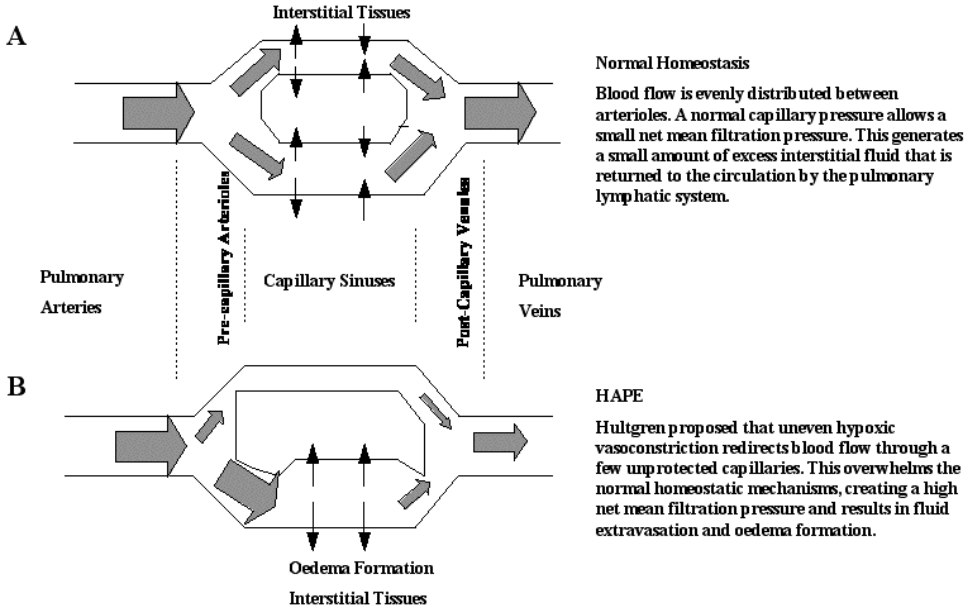

Fig 1. Schematic representation of Hultgren's model of uneven hypoxic pulmonary vasoconstriction. Blood flow is depicted by the block arrows and trans-capillary flow by the simple arrows.

Endothelin-1 and Disease

Raised plasma concentrations of endothelin-1 have been identified in chronic heart failure (Pacher et al, 1993)(Wei et al, 1994), renal failure (Koyama et al, 1989)(Warrens et al, 1990), myocardial infarction (Omland et al, 1994)(Miyauchi et al, 1989) and both primary and secondary pulmonary hypertension (Stewart et al, 1991). Allen and colleagues demonstrated that plasma endothelin-1 concentrations in children with primary pulmonary hypertension correlated with hypoxic pulmonary vasoreactivity (Allen et al, 1993). Although an increase in plasma endothelin-1 concentrations may simply reflect disease progression, there is increasing evidence to support a role for endothelin-1 as a mediator of disease. Increased endothelin-1 gene expression has been identified in endothelial cells from the pulmonary vasculature of patients with primary pulmonary hypertension and experimental pulmonary hypertension (Giaid et al, 1993). In addition, the ratio of arterial to venous concentrations of endothelin-1 is significantly greater than unity, suggesting that the pulmonary circulation generates more endothelin-1 than it clears (Stewart et al, 1991).

HAPE

HAPE is a condition that occurs in individuals who fail to acclimatise to altitudes above 2500m. Victims complain initially of dyspnoea, a dry, but later, productive cough, and fatigue. Clinical examination reveals tachypnoea, tachycardia, a mild fever and coarse inspiratory crepitations (Schoene, 1985). HAPE is rapidly progressive and unless urgent treatment is instituted leads to the development of pulmonary oedema, coma and death. Treatment is aimed at increasing arterial pO2 and the current recommended therapy is rapid descent, supplementary oxygen and administration of the calcium channel blocker, nifedipine.

Endothelin-1 and High Altitude

There is now convincing evidence that the pulmonary circulation plays an important role in the process of acclimatisation and the development of HAPE. Raised pulmonary artery pressure (PAP) is characteristic of humans exposed to high altitude. Individuals who develop HAPE have more pronounced hypoxaemia and pulmonary hypertension than those who are acclimatised (Hultgren et al, 1964)(Scherrer et al, 1996). This increase in pulmonary artery pressure occurs in the absence of either systemic hypertension or symptoms of left ventricular failure and the pulmonary wedge pressure is normal or low (Hultgren, 1996). Hypoxia induces an increase in pulmonary vascular resistance in the arterial segments upstream from arterioles 30-50mm in diameter (Nagasaka et al, 1984). This would suggest that pulmonary vasoconstriction at high altitude occurs at the level of small resistance arteries within the pulmonary circulation (Anand, 1994). Administration of inhaled nitric oxide at high altitude reduces PAP, reverses hypoxaemia and relieves the symptoms of HAPE supporting the hypothesis that excessive vasoconstriction plays a significant role in the pathogenesis of HAPE. (Scherrer et al, 1996).

It is not clear why precapillary pulmonary vasoconstriction should result in the formation of alveolar oedema in HAPE. Hultgren proposed that hypoxic pulmonary vasoconstriction occurs unevenly throughout the lungs shunting blood from poorly ventilated, hypoxic areas to the relatively oxygen rich regions and reducing any ventilation-perfusion mismatch. The additional flow in these unprotected capillaries is then too great and results in endothelial damage and oedema formation (Hultgren et al, 1971). Bronchoalveolar lavage studies have demonstrated that HAPE fluid, rich in high molecular weight proteins and red blood cells, is characteristic of a leaky pulmonary capillary endothelium (Schoene et al, 1988). Stress studies have demonstrated that pulmonary endothelium exposed to high transmural pressures undergoes similar ultrastructural changes to those found in models of HAPE (West et al, 1995).

Plasma concentrations of endothelin-1 are elevated at high altitude and pulmonary artery pressure correlates with endothelin-1 concentrations and inversely with arterial pO2 (Goerre et al, 1995)(Morganti et al, 1995). Reinhart and colleagues further demonstrated that increasing the concentration of inspired oxygen at high altitude to 35% reduced plasma endothelin-1, pulmonary artery pressure and normalised arterial pO2. Although raised levels of endothelin-1 have been demonstrated at high altitude in acclimatised individuals, its role in HAPE has yet to be defined. One group reported raised plasma endothelin-1 in a single patient suffering from HAPE after evacuation to low altitude (Droma et al, 1996). Plasma endothelin-1 concentration fell to within the normal range following the patient's recovery.

Chronic exposure to hypoxia is associated with structural changes in the terminal portions of the pulmonary bronchial tree with muscularisation of the small pulmonary arterioles. These changes are found both in natives of high altitude (Heath and Williams, 1995) and patients suffering from cor pulmonale (Wilkinson et al, 1988). Endothelin-1 is known to have co-mitogenic properties (Wang et al, 1994) and chronic elevation of endothelin-1 concentrations may be important in

remodelling of the pulmonary vasculature.

Clearly, an alteration in endothelial function occurs in the pathogenesis of HAPE. Whether this change is responsible for the development of this life-threatening condition or occurs as an epiphenomenon is not yet known.

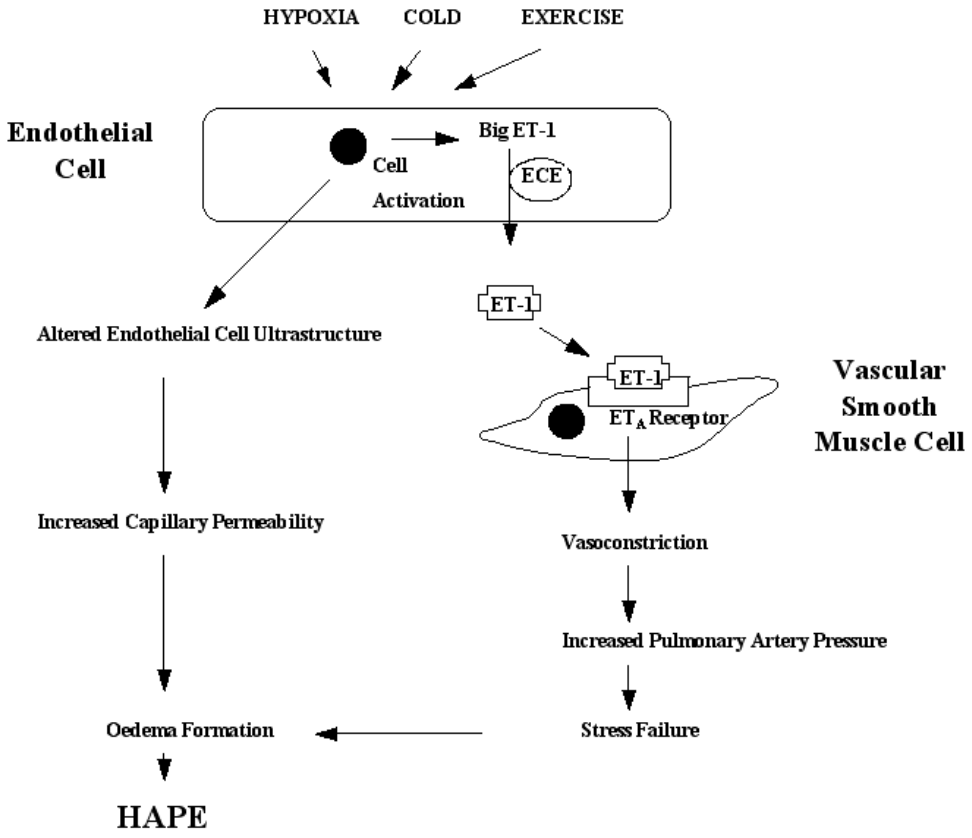

Fig 2. Proposed model for the role of endothelin-1 in the pathogenesis of HAPE
(ECE Endothelin Converting Enzyme, ET-1 Endothelin-1)

Compounding Factors at High Altitude

Mountaineers at high altitude are exposed to hypoxia, freezing temperatures and arduous physical exercise. The contribution made by cold exposure and exercise to the increase in endothelin-1 at high altitude is unclear.

Brief limb immersion in ice-cold water elevated venous endothelin-1 levels in one study (Letizia et al, 1995a) and had no effect in another (Fyhrquist et al, 1990). Whole body exposure to temperatures of 4-12°C for up to 90 minutes did not alter endothelin-1 levels (Matsuda et al, 1992). We have found that whole body exposure to freezing temperatures (-20°C) for 2 hours and exposure to non-freezing cold (+4°C) for 5 hours but not after 2.5 hours significantly increased plasma endothelin-1 (Cruden et al, 1997).

The effect of exercise on plasma endothelin-1 appears to be dependent on the intensity of the exercise undertaken. Two groups have reported no change in endothelin-1 levels in healthy individuals undergoing a graded exercise test lasting up to 15 minutes (Letizia et al, 1995b)(Predel et al, 1995), whereas moderate to heavy exercise lasting 30 minutes or more increased endothelin-1 concentrations

(Maeda et al, 1994)(Ahlborg et al, 1995).

Treatment Implications
The current recommended treatment for HAPE is immediate descent, supplementary oxygen and administration of nifedipine. Nifedipine, a calcium channel blocker, is effective both in the prevention and treatment of HAPE, lowering pulmonary arterial pressure, increasing arterial pO2 and reducing alveolar oedema (Oelz et al, 1989)(Bärtsch et al, 1991). Inhaled nitric oxide has shown similar benefits in the treatment of HAPE but at present, its use is impractical in the high altitude setting (Scherrer et al, 1996).

The emergence of a possible role for endothelin-1 in the pathogenesis of HAPE offers an exciting opportunity to develop new therapeutic strategies aimed at both preventing and treating this serious condition. Systemic administration of combined ETA/ETB receptor antagonists lowered blood pressure in healthy volunteers (Haynes et al, 1996) and patients with essential hypertension (Schmitt et al, 1995). Similarly, in patients with chronic heart failure systemic administration of bosentan, an ETA/ETB receptor antagonist, produced systemic and pulmonary vasodilatation, reduced mean arterial, pulmonary arterial, right atrial and pulmonary artery wedge pressures (Kiowski et al, 1995).

Finally, the development of endothelin converting enzyme inhibitors may provide a further opportunity to modify the endothelin system. The non-specific endothelin converting enzyme inhibitor, phosphoramidon, has been shown to induce local vasodilatation in patients with heart failure (Love et al, 1996). Further work is required to investigate the role of endothelin receptor antagonists and endothelin converting enzyme inhibitors in high altitude-induced pulmonary hypertension and HAPE. Current evidence strongly supports the development of a selective ETA receptor antagonist for this life-threatening clinical condition.

Conclusion
There is no doubt that the pulmonary circulation plays a key role in human acclimatisation to high altitude and the development of HAPE. The mechanism by which these changes are mediated is not clear but there is increasing evidence to support the involvement of the potent vasoconstrictor, endothelin-1. There are a number of novel endothelin antagonists that may be effective in the treatment of HAPE. Clinical trials are required to investigate the role of these compounds in the process of acclimatisation to high altitude and the management of HAPE.

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