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CHRONIC HYPOXIA MODULATES ENDOTHELIUM-DEPENDENT VASORELAXATION THROUGH MULTIPLE INDEPENDENT MECHANISMS IN OVINE CRANIAL ARTERIES

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1. INTRODUCTION

Of the many external physiological perturbations that may alter blood O_2 transport, chronic hypoxia is probably the most widely studied. Chronic hypoxia is a challenge not only for mountain climbers and pilots, but also for patients with respiratory disease and fetuses compromised by placental insufficiency. Motivated by this clinical relevance, numerous studies have detailed the effects of hypoxic adaptation. Because physiological stresses that influence O_2 delivery stimulate homeostatic responses not only in blood composition, but also in the blood vessels that serve at the interface between oxygen supply and demand, many studies have examined hypoxic modulation of vascular composition and function[1-6]. For example, high altitude acclimatization has been shown to alter vascular protein content, contractility, receptor profile, and perivascular nerve function[7-9]. Aside from the intense attention focused on the effects of hypoxia on vascular contractility, however, comparatively little scrutiny has been directed toward the effects of chronic hypoxia on mechanisms of vasorelaxation. This is somewhat surprising, given that vasodilatation is a key initial response to acute hypoxia in most vascular beds[10, 11]. In particular, the effects of chronic hypoxia on endothelial vasodilator function remain largely unexplored, even though the endothelium may significantly augment vasodilator responses to acute hypoxia[12]. The present study was designed to address this deficit.

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2. MECHANISMS OF ENDOTHELIUM-DEPENDENT VASODILATATION

To examine the effects of chronic hypoxia on endothelial vasodilator function, we used common carotid arteries taken from young non-pregnant adult sheep that had been maintained for 110 days at an altitude of 3820 m. The arteries were mounted in tissue baths for measurements of contractile responses, as previously described in detail[7, 12]. To enable the study of relaxation responses, the arteries were first contracted with 1 μM serotonin, which is approximately the EC_{50} concentration in this preparation[13]. To stimulate endothelium-mediated vasorelaxation, we treated the arteries with 1 μM A23187. This calcium ionophore facilitates calcium entry into endothelial cells in a receptor-independent manner, and is thus highly useful for maximally stimulating endothelial NO release[14]. To verify that all A23187-induced relaxation was due to activation of the enzyme eNOS (endothelial nitric oxide synthase), we also verified that treatment with 100 μM L-Nitro-Arginine Methyl Ester (L-NAME) could completely block all responses to A23187 (see Figure 1).

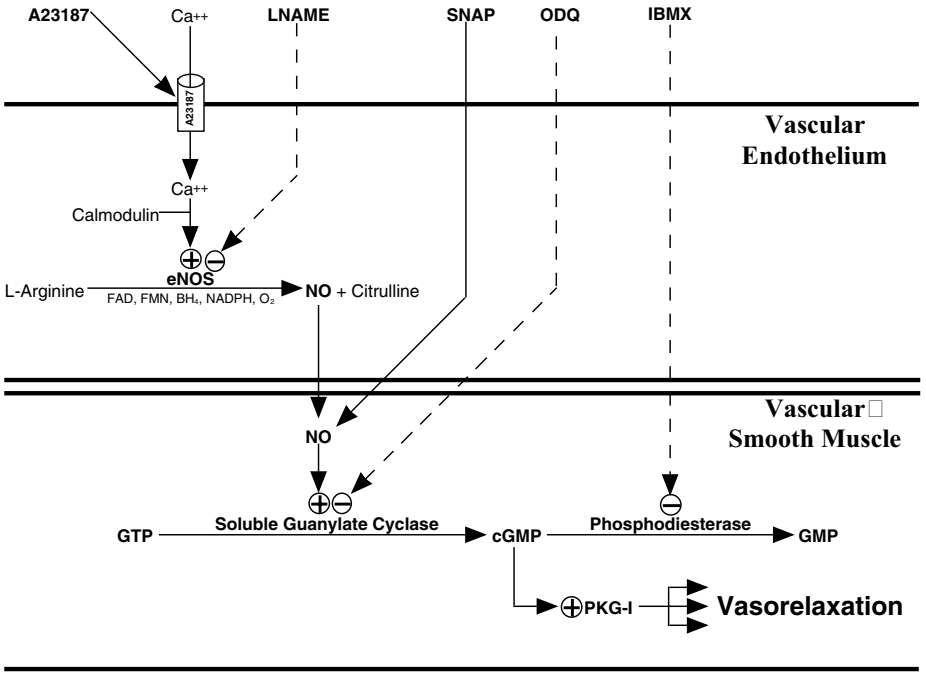

Figure 1. Endothelium-dependent vasodilatation is initiated by a rise in endothelial calcium concentration, which in turn stimulates the enzyme eNOS to synthesize and release NO. The NO is synthesized from L-Arginine and requires the cofactors FAD, FMN, BH4, NAPDPH, and O_2. This NO then diffuses into adjacent smooth muscle where it binds to the heme moiety on soluble guanylate cyclase and activates the synthesis of cGMP from GTP. This cGMP then combines with protein kinase G (PKG) to promote vasorelaxation through multiple mechanisms until is it hydrolyzed by phosphodiesterase. Please see text for additional details.