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Effect of protein arginine methyltransferase-1 inhibition on hypoxia-induced vasoconstriction

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ABSTRACT

Hypoxia is defined as a decrease in the oxygen supply to a level below physiological levels which is insufficient to maintain cellular function, in the presence of unrestricted coronary inflow. It is one of the leading causes of global mortality and morbidity, due to its association with the pathology of cancer, cardiovascular disease and stroke. The common feature in these pathologies is the limitation of oxygen availability that participates in the development of these conditions. The pulmonary response to hypoxia, when hypoxia is localized, is hypoxic pulmonary vasoconstriction (HPV). HPV is a physiological and self-regulatory mechanism by which pulmonary capillary blood flow is automatically adjusted to alveolar ventilation for maintaining the optimal balance of ventilation and perfusion. In pathological conditions, HPV occurs as an acute episode during progressive critical illness or as a sustained response with vascular remodeling and pulmonary hypertension. Inspite of the hypoxia-induced shift in the redox status to a more oxidized state, the endothelium-dependent mediators of HPV that cause vasoconstrictor response to hypoxia include nitric oxide (NO), endothelin-1 and angiotensin-II. Indeed, in chronic hypoxia, due to the enhanced reactive oxygen species (ROS) generation, inhibition of endothelial nitric oxide synthase (eNOS) activity and reduced nitric oxide (NO) production there is an imbalance in the vasoconstric tion–vasodilation status toward constriction. It is our hypothesis that, in hypoxic stress, a key player in initiating this imbalance is the enzyme, protein arginine methyltransferase-1 (PRMT1) which indirectly affects eNOS activity by increased production of asymmetric dimethylarginine (ADMA), a NOS-inhibitor. Thus, pharmacological inhibition of PRMT1 should restore the cellular and vascular homeostasis in hypoxic conditions.

Mechanisms that lead to cardiovascular distress in chronic hypoxia

Hypoxia is a condition defined by the reduction in oxygen supply to cells and tissues at concentrations insufficient for sustaining normal metabolic functions. Intermittent hypoxia may be beneficial to pulmonary and respiratory functions but in chronic conditions, it leads to deterioration of the physiological functions [1]. Hypoxia is associated with HPV, the physiological condition where pulmonary arteries constrict to moderate hypoxia. HPV is a protective mechanism which is responsible for maintaining the ventilation–perfusion ratio during localized alveolar hypoxia. In disease states, however, HPV results in a detrimental increase in total pulmonary vascular resistance and increased load on the right heart [2]. This pathophysiology is often observed in other hypoxia related disorders such as disruptive sleep apnea and acute mountain sickness in which a high incidence of cardiovascular disease occur [3]. The precise mechanisms underlying HPV remain unclear, yet, HPV has an endothelium dependency [2]. The mechanisms behind constriction and relaxation of vascular endothelium are explained in terms of ROS and NO [4]. ROS serve as an integral component of cellular signaling pathways [5] and they promote vasoconstriction [6]. Nonetheless, when these highly reactive metabolic products are in excess, they impose an oxidant stress on the cellular environment, leading to pathologic cell responses [7]. In physiological conditions, ROS are produced by mitochondria and antioxidant enzymes balance its physiological equilibrium [8]. However, in pathological states other mechanisms of ROS production such as uncoupled eNOS, xanthine oxidase and NADH/NADPH oxidase come into action leading to excess intracellular ROS [7]. Hence, although paradoxical, hypoxia leads to increased intracellular ROS production [9,10].

Nitric oxide, a potent vasodilator, on the contrary to that of ROS has a physiological role [11,12]. Studies demonstrate that impaired

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endothelium-dependent vasodilation is associated with endothelial NO concentration, cardiovascular disease risk factors, and atherosclerosis [13]. The enzyme, eNOS is the primary source of NO [14] which is crucial in preserving vascular homeostasis by maintaining NO concentrations in equilibrium with ROS. While, eNOS in its physiologically functional state maintains the NO–ROS balance, uncoupled eNOS, impaired nitric oxide bioavailability and excess ROS are the molecular signatures in the pathogenesis of cardiovascular disease [4,15], as depicted in Fig. 1. Though it is evident that oxygen influences the NO–ROS equilibrium *via* regulating eNOS activity, it does have an effect on caveolin-1, the signaling partner and a negative regulator of eNOS, that modulates pulmonary vasodilation [16]. The enzyme activity of eNOS is mainly controlled by posttranslational modifications, such as protein–protein interactions, subcellular localization in specialized compartments, and phosphorylation [17,18]. Importantly, eNOS binding with caveolin-1 by a specific protein–protein interaction targets eNOS into the caveolae, rendering it inactive [19]. Hypoxia in pathological conditions is known to cause an adverse decrease in intracellular NO levels by inhibiting the enzyme activity and function of eNOS [20]. Moreover, hypoxia enhances the caveolar compartmentalization of eNOS by up-regulating the association between eNOS and caveolin-1 which attenuates eNOS activity [21]. Extending equally, hypoxic stress depletes the concentration of eNOS cofactor, tetrahydrobiopterin, leading to eNOS uncoupling, wherein eNOS becomes a superoxide generating enzyme rather than NO [21]. Chronic hypoxia increases the post translational modification of L-arginine by protein arginine methylation and a subsequent increase in ADMA levels [23]. ADMA, the endogenous inhibitor of nitric oxide synthase (NOS) [22], is an analog of L-arginine and is a naturally occurring product of metabolism found in human circulation. Elevated levels of ADMA inhibit NO biosynthesis which impairs the physiological endothelial function to promote atherosclerosis [24]. Hence, increased concentration of plasma ADMA is another predictive of cardiovascular events. Protein arginine methyltransferase-1 is the enzyme that catalyzes ADMA formation wherein it methylates proteins on the guanidino nitrogen atom of the arginine residues. In point of fact, PRMT1 is the predominant isoform of all PRMTs that exists within the nucleus and in the cytoplasm performing various functions including transcriptional activation and regulation of gene expression [25]. Studies demonstrate that under chronic hypoxic stress, ADMA level is up-regulated and that chronic hypoxia in pathological conditions is a potent trigger that accelerates the expression and activity of PRMT1 and eventually arginine methylation to increase plasma ADMA levels [23]. Increase in ADMA concentration leads to inhibition of eNOS activity and disruption of NO–ROS balance. This relative increase in ROS contributes to vasoconstriction as well as inhibition of dimethylarginine dimethylaminohydrolase (DDAH), the ADMA-metabolizing enzyme, which results in accumulation of ADMA [Fig. 2; 16,26], [27]. Due to this positive feedback loop, adverse events occur, which includes eNOS uncoupling, endothelial damage and eventual arteriosclerosis that leads to cardiovascular disease, a distinctive feature of chronic hypoxia (Fig. 1). Since the available therapeutics for hypoxia lacks a sustained effect, pharmacological approach to address pathological hypoxia in terms of restoration of equilibrium in either NO: ROS or vasodilation:vasoconstriction is yet to be identified. Therefore, we presume that pharmacological inhibition of PRMT1 will address the hypoxia-induced vascular distress such as pathological HPV, by targeting the source of the complication, NO–ROS balance, at the cellular level. The rationale for this approach can be summarized as follows: (i) To restore the eNOS activity to physiological levels, (ii) To restore the balance between NO and ROS concentrations, thereby re-establish the symmetry in vasodilation and vasoconstriction and (iii) To establish the vasoprotective effects of PRMT1 inhibition in severe hypoxic conditions. Manifestation of symptoms and progression of disease is not the same for every individual afflicted with chronic hypoxia, therefore the degree of treatment may vary depending upon the disease pathology.

Hypothesis

Pharmacological inhibition of PRMT1 will ameliorate the pathological effects of hypoxia in HPV, by re-establishing a balance in NO and ROS concentrations; by restoring the physiological ADMA concentration and enzyme activity of eNOS. Inhibition of PRMT1 will address the vascular pathologies that are caused due to ADMA accumulation, impaired eNOS function, diminished NO bioavailability and excess ROS concentration. Thus, PRMT1 inhibition will prevent hypoxia-induced cell senescence and vascular dysfunction.

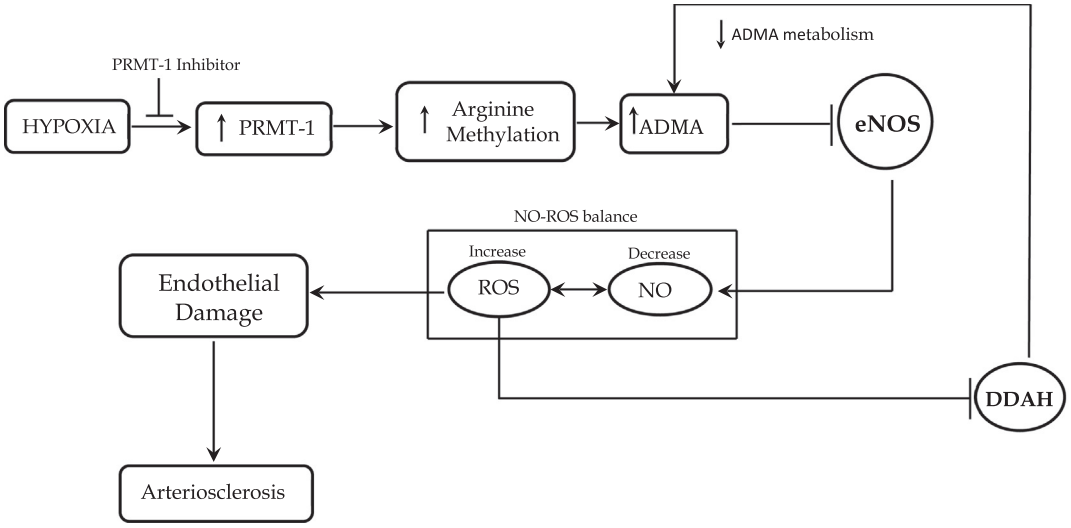

Fig. 1. Proposed scheme of the effect of PRMT1 inhibition on hypoxia. Hypoxic stress enhances asymmetric dimethylarginine (ADMA) production, catalyzed by protein arginine methyltransferase-1 (PRMT1), to uncouple endothelial nitric oxide synthase (eNOS) and generate reactive oxygen species (ROS) rather than nitric oxide (NO). Up-regulated ADMA and ROS generation causes dimethylarginine dimethylaminohydrolase (DDAH) inhibition, endothelial damage and vascular disease. Measurement of ADMA, PRMT1 and NO in the presence or absence of a PRMT1 inhibitor would reflect the therapeutic potential of PRMT1 inhibition in hypoxic stress.