ABSTRACT

In the healthy lung, a high-flow, low-resistance vascular bed characterizes the pulmonary circulation. A balance between endothelium-derived relaxing factors and constricting factors such as endothelin 1 (ET-1) maintains this state. ET-1 has been found to play an important role in not only the development of both primary and secondary pulmonary hypertension but also in the pathophysiology of other diseases including congestive heart failure, renal failure and cerebrovascular disease. Experimental data suggest that free radicals and ET-1 play important roles in many lung diseases. The lungs represent a primary target for ET-1 effects and are a special site for ET-1 metabolic pathways. Free radicals cause pulmonary vascular wall injury, which then leads to vascular proliferation and structural remodeling. It has been shown that oxidative stress is increased in patients with pulmonary hypertension as the levels of lipid peroxidation as assessed by isoprostane (iPF2a-III), are increased and inversely correlated with pulmonary vasoreactivity. These suggest that free radical generation is involved in pulmonary hypertension pathogenesis. That free radicals are involved then indicates that the antioxidant defense system is of importance.

This antioxidant system involvement then provides a link between the metabolism of vitamin E (the most studied lipid soluble antioxidant) and ET-1. The alteration of the physiological vitamin E (alpha-tocopherol) concentration and metabolism will affect the cellular redox state with an increase of reactive oxygen species (ROS) and lead to oxidative stress. These increased oxidants will activate the redox sensitive transcription factor NFkB which in turn downregulates scavenger receptor B1 (SR-B1). Decreased SR-B1 should lead to further declines in cell alpha-tocopherol (a-Toc) given SR-B1's role in tocopherol delivery and uptake. Decreased cell a-Toc should reduce tocopherol activation of peroxisome proliferator-activated receptor gamma (PPARg) which should then diminish PPARg inhibition of CD36 expression and NFkB. CD36 should increase with decreased PPARg activation, which should then result in increased CD36. Increased CD36 expression should then lead to increased ET-1 which should lead to increased oxidants.