SYMPOSIA

Free Radical Mechanisms of Cellular Injury Symposium: Introduction

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*On February 17, 1999 a joint symposium was organized by the District of Columbia Section of the *Society for Experimental Biology and Medicine and †Oxygen Club of Greater Washington, D.C.*

Free radical generation, including reactive nitrogen and reactive oxygen species, is known to participate in cell physiology in both a positive and negative manner. Moreover, alterations in their concentrations are implicated in a number of human diseases. Two of the talks in this mini symposium discussed research on nitroxides and the third talk addressed the clinical application of controlling free radical concentrations. Dr. David Wink eloquently discussed the chemistry of nitric oxide (NO) in the attempt to understand the mechanisms of NO reactivity during pathophysiological events. Such understanding may open the door to therapeutic applications. He specifically reviewed the indirect effects that are mediated by reactive nitrogen oxide species and talked about nitrosative and oxidative stress. Dr. James Mitchell presented data (*in vitro* as well as *in vivo*), and chemical explanations showing how non-toxic levels of nitroxides can actually act as protectors against oxidative damage. Dr. Mitchell's research also involves testing the feasibility of using nitroxides and other paramagnetic probes for *in vivo* electron paramagnetic resonance imaging. The latter allows the study of probe uptake, oxygen content in tissues, and tissue redox reactivity. Dr. Christopher Wilcox discussed the clinical potential of controlling free radical reactions. He used the spontaneously hypertensive rat (SHR) as a model of oxidative stress. The data showed oxidative stress may adversely affect normal epithelial-vascular signaling between the macula densa and afferent arteriole of the kidneys in SHR, thereby inducing pre-glomerular vasoconstriction and salt sensitivity and hypertension. Long-term data using a superoxide dismutase agonist support the possibility of developing this category of compounds as a novel therapeutic approach to lower renal vascular resistance and blood pressure, as well as restoring normal blood vessel physiology.

Oxidative Stress: Cause or Consequence of Hypertension

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Studies in the blood vessel of animal models of hypertension have shown that oxidative stress can impair the normal physiologic transmission through vasodilator pathways linking the endothelium to the adjacent vascular smooth muscle cells. Reactive oxygen species (ROS) found in the wall of the aorta and major conduit vessels in animals with genetic or renovascular hypertension constitute an endothelium-derived constrictor factor that diminishes the half-life of the endothelium-derived nitric oxide (NO) and can irreversibly inactivate prostacyclin synthase. Furthermore, oxygen radicals can directly oxidize free or esterified arachidonate to form isoprostanes that can engage vasoconstrictor and prothrombotic mechanisms via the TP receptor. These vasoconstrictive, prothrombotic and atherosclerotic pathways linked to ROS are well established in large vessels, where they may contribute to the atherosclerosis. However, their importance in the regulation of peripheral vascular resistance and specifically in the resistance of the preglomerular afferent arterioles in the kidney remains elusive. This has been the focus for our studies.

The afferent arterioles of the kidney contain more than 95% of the rennin secreted by the kidney. They are also the