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THE ROLE OF NITRIC OXIDE IN CELL RESPIRATION: PHYSIOLOGY AND PATHOPHYSIOLOGY

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Nitric oxide (NO) is a ubiquitous signaling molecule whose physiological roles mediated through the activation of the soluble guanylate cyclase are now clearly recognized. At physiological concentrations, NO also inhibits the mitochondrial enzyme cytochrome c oxidase (complex IV) in competition with oxygen and we have suggested that the interplay between the two gases allows this enzyme to act as an oxygen sensor in cells. In addition, NO plays a variety of pathophysiological roles, some of which also may be the consequence of its action at a mitochondrial level. Our work has characterized the sequence of events that follow inhibition of complex IV by continuous exposure to NO. We have found that oxidative stress develops with the subsequent inhibition of other mitochondrial and cytosolic enzymes. We have suggested that in this way NO may progress from acting as an important physiological regulator of cell respiration to becoming an agent of cell pathology.

We have recently shown in Jurkat cells that inhibition of respiration by exogenous NO leads to mitochondrial membrane hyperpolarization dependent on the utilization of glycolytic ATP by the F_1F_0-ATPase and other transporters acting in reverse mode. This process also occurs in astrocytes,which are highly glycolytic cells, but not in neurons, which do not invoke glycolysis to maintain ATP concentrations. In addition, we have demonstrated that this hyperpolarization correlates with protection against apoptotic cell death. As a result of these observations we have speculated that endogenous NO released during cellular stress may trigger such a defence response.