

P005 Nitrosation of mitochondrial complex I depends on conformation of the enzyme

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Nitric oxide is known to cause persistent inhibition of mitochondrial respiration as a result of S-nitrosation of NADH:ubiquinone oxidoreductase (complex I). Little is known about whether such nitrosation occurs in physiological conditions and, if so, what are the possible cellular mechanisms. We have now found that the conformational state (active or de-active) of mitochondrial complex I is an important factor for the interaction of the enzyme with nitrosothiols and peroxyxynitrite since only the de-activated, dormant form of complex I was susceptible to inhibition by these nitrosating agents. The active form of the enzyme was insensitive to such treatment. Neither form of complex I was inhibited by nitric oxide itself. Our data suggest that the conformational state of complex I plays an important role in the regulation of enzyme activity and cellular respiration by nitric oxide. The slowing down of the activity of mitochondrial respiratory chain in hypoxic conditions leads to de-activation of complex I and consequent modification by nitrosating agents, so that transition to the active form is arrested and the enzyme becomes locked in its dormant form. Such locking of complex I in the dormant form may have severe pathophysiological consequences which would depend on the duration of hypoxia, type of tissue and presence of natural effectors of active/de-active transition such as calcium and free fatty acids.