However, under a range of pathological conditions NO levels can rise to micromolar levels and disrupt a wide range of cellular processes. Between these two extreme concentration ranges NO can interact with mitochondria in ways that have been described as physiological or pathophysiological. The highest affinity target is cytochrome *c* oxidase. This talk will review this interaction and suggest that it has the potential to play a role in both NO signalling and detoxification. NO has also been shown to interact with lower affinity with mitochondrial cytochrome *c* in both its reduced and oxidised forms. Previous studies have indicated that NO can oxidise cytochrome *c* at physiological pH. We show that most of this oxidation is not caused by direct reactions of NO, but instead by a reaction product of NO and oxygen, most likely NO_2. In contrast the reaction of NO with oxidised cytochrome *c* is a direct, reversible binding. Intriguingly in the presence of cardiolipin NO can also bind reduced cytochrome *c* with high affinity at neutral pH. We will describe these interactions and comment on their biological relevance.

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S10/2 Mitochondria and reversible apoptosis

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Apoptosis has been considered as a form of cell death, to which a cell is irreversibly committed once cytochrome *c* is released from the mitochondria. However, apoptosis can also be regarded as a means of signalling to phagocytes, which may in principle be reversible up to the point of phagocytosis. We find that mitochondrial cytochrome *c* release does not inevitably commit a cell to death because if the cell reduces the cytosolic cytochrome *c* then caspase activation is blocked. Similarly caspase activation does not inevitably commit a cell to death, because the caspases can be inactivated by endogenous oxidants. Phosphatidylserine flip to the outer leaflet of the plasma membrane is also a reversible process, as long as phagocytes are not present to eat the cell. We find that many aspects of apoptosis are fully reversible in neurons. This leads to the conclusion that apoptosis can (in some circumstances) be reversible and is not always a form of cell death.

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S10/3 Ischemic preconditioning invokes multiple mechanisms of nitric oxide and reactive oxygen signaling at the mitochondrial level

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Ischemic preconditioning (IPC) is a phenomenon in which short cycles of ischemia and reperfusion (IR) can protect organs such as the heart and brain from prolonged IR injury. Mounting evidence suggests that both mitochondria and nitric oxide play critical roles in IPC signaling, although the exact biochemical mechanisms underlying cardioprotection are poorly understood. We have identified 3 novel biochemical events involving reactive oxygen and nitrogen species, which may contribute to the modulation of mitochondrial function in IPC: (1) *S*-nitrosation and reversible inhibition of respiratory chain complex I. (2) Activation of mild uncoupling via the generation of NO derived electrophilic lipids (nitro-alkenes) and their post-translational modification of mitochondrial carrier family proteins. (3) Endogenous generation of mitochondrial K^+_{ATP} channel agonists and complex II inhibitors, via redox reactions involving Krebs' cycle intermediates. Together, it is thought that these 3 pathways all act to diminish mitochondrial Ca^{2+} overload and ROS generation at reperfusion, thereby limiting the opening of the permeability transition pore. A brief outline of the key findings in support of these novel signaling pathways will be discussed.

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(S10) Mitochondria and reactive oxygen containing species symposium abstracts (poster and raised abstracts)

S10.4 Mild uncoupling reduces oxidative stress in intact cells

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"Mild uncoupling", the introduction of a limited proton conductance into the mitochondrial inner membrane, has been demonstrated to greatly reduce reactive oxygen species (ROS) production in isolated mitochondria. On the other hand, it will also increase energy consumption to maintain the mitochondrial membrane potential, and cells need energy in the form of NADH to maintain the cellular protein machinery in the normal, reduced state. For this reason it has been a subject to debate whether mild uncoupling is a viable strategy to reduce oxidative stress in intact cells and ultimately in vivo, or whether the increased energy expenditure might have detrimental effects. Using a redox-sensitive green fluorescent protein (roGFP1) targeted to mitochondria of PC12 cells, we found that mild uncoupling using low concentrations of chemical uncouplers FCCP or DNP indeed reduced oxidative stress, whereas strong uncoupling caused oxidation of roGFP1, indicating that the beneficial effects of uncoupling are limited to a certain range of membrane potential, and that uncoupling beyond this range will increase oxidative stress probably due to energy crisis. This leads to the conclusion that while mild uncoupling might be beneficial under some circumstances, it is a dangerous strategy since the safe range of uncoupling will probably depend on cell type and metabolic state.

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S10.5 The role of reactive oxygen and nitrogen species in the pathogenesis of acute renal failure

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The aim of this work was to study mechanisms of acute renal failure (ARF) development in kidney survived ischemia or mioglobinuria (rabdomyolysis). Experimental model of those pathologies showed that 3 days after ischemia or induction of rabdomyolysis, the levels of urea, creatinine and cell death markers increase. Such kidney malfunctioning can be caused by tubular epithelium destruction. In our experiments, lipid peroxidation products accumulated in kidney and total antioxidant activity of blood are decreased. Also the level of nitrite in blood serum was increased indicating the activation of NO production. Analysis of ROS- and NO-production in kidney cells revealed amplification of the production of these radicals. We