high $_eK^+$ (1–12 min after treatment with EGTA) had an additive effect on cellular $O_2$ consumption, reducing $_iO_2$ to 60% of air saturation. The respiratory response was accompanied by $Na^+$ influx, a decrease in cytosolic and mitochondrial $Ca^{2+}$ and partial depolarization of plasma membrane, while the mitochondrial membrane potential (MMP) and cellular ATP remained unchanged. The effect of EGTA was down-regulated by the depletion of $Ca^{2+}$ stores and dissipation of proton gradient across the mitochondrial membrane, up-regulated by mitochondria uncoupling and was independent on MMP. The respiratory effect was largely reduced by the inhibition of mitochondrial $Na^+/Ca^{2+}$ exchanger ($_mNCX$) and $Na^+/H^+$ exchangers. We suggest that such respiratory response is driven by a non-selective $Na^+$ influx, activation of $_mNCX$ and increased mitochondrial $Na^+/H^+$ exchange. This leads to the acidification of matrix, loss of $_mCa^{2+}$ and acceleration of mitochondrial proton pumps to restore proton gradient.

doi:10.1016/j.bbabio.2008.05.186

### S7.10 Bioenergetics and mitochondrial transport in hippocampal neurons

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Impaired transport of mitochondria in neurons and bioenergetic deficit are increasingly recognized to be of pathological importance in neurodegenerative diseases. To study the relationship between transport and bioenergetics we have developed a novel image processing technique to quantify organelle velocity in cultured cells. This combines measurement of motion and bioenergetic parameters while minimizing photodynamic oxidative artifacts evoked by fluorescence excitation. To describe populations of mitochondria in resting cultured hippocampal neurons in addition to motion analysis, measurements of mitochondrial thiol redox status by mitochondrially-targeted redox-sensitive GFP and mitochondrial membrane potential by TMRM were performed. Mitochondria with more oxidized thiol redox status had lower membrane potentials and were smaller in size. These mitochondria were more motile than the average, however mitochondrial motility was only slightly dependent on the observed bioenergetic parameters, and correlated the best to their size. Mean velocities of mitochondria were unaltered by glycolytic inhibition and decreased by inhibition of oxidative phosphorylation. To stop motion cessation of both ATP sources was required. Depolarization of mitochondria when the ATP-synthase was inhibited did not further decrease the mean velocity and affect the directionality of the motion. It is concluded that mitochondrial motors respond to the global ATP level, which is mainly determined by the oxidative phosphorylation. The mitochondrial membrane potential does not regulate mitochondrial transport in hippocampal neurons.

doi:10.1016/j.bbabio.2008.05.187

### S7.11 Metabolic control analysis of bioenergetic function in synaptosomes

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The aim of this study was to use metabolic control analysis (MCA) to examine the spread of control amongst the electron transport chain (ETC) complexes over the process of mitochondrial oxidative phosphorylation in rat brain synaptosomes. Oxygen consumption and ETC activities were titrated with appropriate inhibitors to determine the flux control coefficients and the energy threshold levels. The flux control coefficients for complex I, complex II/III and complex IV were found to be 0.30, 0.20 and 0.19, respectively and the energy thresholds for complex I, complex II/III and complex IV were determined to be ~15%, ~35 and ~30%, respectively. These results indicate that complex I exerts a high level of control over synaptosomal bioenergetics, suggesting that complex I deficiencies in neurodegenerative disorders, such as PD, may compromise mitochondrial oxygen consumption in the nerve terminal, possibly leading to neuronal dysfunction. In addition, the effect of coenzyme Q on the flux control coefficient and energy threshold effect of complex I was examined. No statistically significant difference in flux control coefficients and energy thresholds for complex I was found, however, during titration of complex I activity with rotenone the presence of coenzyme Q decreased the rate of inhibition of oxygen respiration. These results suggest that complex I in the nerve terminal possess sensitive control over mitochondrial respiration rates and may be a therapeutic target for neurodegenerative conditions in which complex I activities are decreased.

doi:10.1016/j.bbabio.2008.05.188

## (S8) Mitochondria and cell physiology symposium lecture abstracts

### S8/1 Iodothyronines and mitochondria

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Studies of the effects of iodothyronines on mitochondria have been focused on T3, but recently other iodothyronines such 3,5-diiodothyronine (T2), have been identified as possible peripheral mediators of the effect of thyroid hormones on cell respiration. In this context, we have shown that T2 powerfully reduce adiposity in high-fat-fed rats by increasing the burning of fats. Now we report that T2 in a short term is able i) to affect mitochondrial fatty acid oxidation rate in skeletal muscle ii) to activate the AMPK-(ACC)-malonyl CoA signalling pathway iii) to affect mitochondrial thermogenesis. The administration of T2 to hypothyroid rats induced an increase in mitochondrial oxidation when palmitoyl-CoA (+104% vs. hypo), palmitoyl-carnitine (+80% vs. hypo) and succinate (+30% vs. hypo) were used as substrates. These results suggest that T2 stimulates mitochondrial fatty acid oxidation by activating more metabolic pathways: -import of fatty acid into the mitochondria–beta oxidation cycle–$FADH_2$ linked respiratory pathways. Indeed, T2 is able to activate the AMPK signalling pathway known to direct lipid partition towards oxidation and to induce the activation of mitochondrial fatty acid import. T2 also enhanced skeletal muscle mitochondrial thermogenesis by activating pathways involved in the dissipation of proton motive force not associated to ATP synthesis ("proton leak"), the effect being