[a]Neurobiology Laboratory for Brain Aging and Mental Health, Psychiatric University Clinic, 4025 Basel, Switzerland
[b]Hoffmann-La-Roche AG, Pharma Research, Neurosciences, 4070 Basel, Switzerland
[c]Center for Biological Chemistry, University of Frankfurt, 60590 Frankfurt, Germany
[d]Alzheimer's and Parkinson's Disease Laboratory, Brain and Mind Research Institute, University of Sydney, 2050 Sydney, Australia
E-mail: virginie.rhein@upkbs.ch

Mitochondrial dysfunction is recognized as earliest event in Alzheimer's disease. To better understand the direct impact of Aβ/tau interplay, Alzheimer's proteins, on mitochondria, we are currently investigating the brains of double (APP (KM670/671NL)/PS2 (N141I)), triple (APP (KM670/671NL)/PS2 (N141I)/Tau (P301L)) and single Tau (P301L) transgenic mice at the age of 2, 4, 7–8, 12 and 16 months. In triple transgenic mice, mitochondrial respiration is reduced compared to double transgenic mice and to single transgenic tau mice at the age of 12 months. In fact, activities of mitochondrial complexes I and IV were decreased as well as membrane potential and ATP levels. On the contrary, ROS production was increased. These effects seem to be age dependent and correlate with the corresponding Aβ and tau histopathologies. Based on these preliminary findings, we conclude that tau and Aβ have synergistic effects on mitochondria. Supported by SNF grant 310000–108223 and Eli Lilly International Foundation grant to AE.

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S12.42 The frataxin-interacting protein GRP75 chaperone plays an essential role in mitochondrial Fe/S cluster biogenesis

Yuxi Shan, Gino Cortopassi
University of California, Davis, USA
E-mail: gcortopassi@ucdavis.edu

The purpose of the study is to identify the pathophysiological consequences of depletion of the mitochondrial protein frataxin. The neurodegenerative disorder Friedreich's ataxia is caused by mutations in frataxin, a mitochondrial protein whose function remains controversial. Our previous work showed that frataxin interacts with GRP75, a homolog of the yeast ssq1 chaperone that integrates iron–sulfur clusters into imported mitochondrial proteins (Shan et al; 2007). Although ssq1′s function has been well characterized in the yeast, the role of GRP75 in Fe–S cluster biogenesis in mammals has never been evaluated. Interactions between frataxin and GRP75 were confirmed by co-immunoprecipitation and GST-pulldown analysis in mammalian cells. GRP75 strongly binds mitochondrial ISCU and mitochondrial Nfs1, two main components of the mitochondrial Iron Sulfur Cluster Assembly machine. Only weak interactions were observed between GRP75 and extramitochondrial ISCU, and no interaction was found between GRP75 and extramitochondrial Nfs1. Endogenous immunoprecipitation analysis confirmed the interaction of GRP75 with mitochondrial ISCU, Nfs1 and Nfu. Upon GRP75 depletion by siRNA in HeLa cells, the amount of the ISCU, Nfu and mitochondrial aconitase protein and aconitase activity declined. GRP75 depletion also increased transferrin receptor levels and cellular iron content, i.e. a phenocopy of frataxin knockdown. These data suggest that the frataxin partner GRP75 functions specifically in mitochondrial iron–sulfur biogenesis, and multiple consequences of GRP75 deficiency are duplicated by frataxin deficiency.

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S12.43 Gene expression profiling of liver and skeletal muscle in newborn mice exposed to an in utero low protein diet with or without taurine

Ole H. Mortensen[a], Hanne L. Olsen[b], Lis Frandsen[a], Peter E. Nielsen[b], Finn C. Nielsen[c], Niels Grunnet[a], Bjørn Quistorff[a]
[a]Department of Biomedical Sciences, University of Copenhagen, Denmark
[b]Department of Cellular and Molecular Medicine, University of Copenhagen, Denmark
[b]Department of Clinical Biochemistry, Rigshospitalet, Denmark.
E-mail: ole@hartvig.org

Fetal nutritional deprivation is associated with increased risk of dysregulation of glucose metabolism in adult life, however the exact mechanism for this is unknown. Neonatal administration of taurine has a beneficial effect on glucose homeostasis in mice in adult life. The aim of the study was to examine if maternal taurine supplementation had an effect upon gene expression patterns in liver and skeletal muscle in newborn mice subjected to a maternal low protein (LP) diet. LP offspring had decreased birth weight, liver mass and muscle mass compared to normal protein (NP) offspring, with taurine supplementation partially rescuing this effect. Changes in mitochondrial genes were found to be overrepresented in both liver and skeletal muscle. LP offspring had a significant change in 451 genes in liver and 330 genes in skeletal muscle compared with NP offspring. Taurine had a rescuing effect on 164 genes (36%) in the liver and 223 genes (68%) in the muscle. In conclusion, maternal taurine supplementation partially rescued changes in body mass and gene expression patterns in liver and skeletal muscle of newborn mice subjected to a maternal LP diet.

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S12.44 Mitochondrial function in lamb as a consequence of maternal caloric restriction during pregnancy and high-fat-high-carbohydrate diet post partum

Wenche Jørgensen[a], Christiane Gam[a], Morten Scheibye-Knudsen[a], Mette O. Nielsen[b], Niels Grunnet[a], Bjørn Quistorff[a]
[a]Department of Biomedical Sciences and Basic Animal and Veterinary Sciences, Denmark
[b]University of Copenhagen, Denmark
E-mail: Wenche@imbg.ku.dk

The aim of this study was to examine effects of foetal programming upon adult life. We examined muscle biopsies from lambs of ewes that were exposed to a low calorie (LC) diet containing only 50% of their normal calorie intake for 6 weeks prior to giving birth. Subsequently half of the lambs were exposed to a high-fat high-carbohydrate (HFHC) diet before they were sacrificed at the age of 6 month. The HFHC diet induced a 50% increase in mtDNA while mitochondrial $VO_{2\,max}$ was decreased, especially in the LC groups. The most pronounced change, however, was a two-fold change in respiratory coupling ratio (RCR) in the group receiving HFHC post partum, independent of the feeding of the mothers. UCP3 mRNA levels were decreased in all groups compared to control. PGC-1α mRNA levels were increased in the LC group independent of HFHC. In conclusion, the increased mitochondrial coupling induced by HFHC feeding will contribute to an increased ROS load and thereby offer a possible mechanism of how such combined effects of intrauterine and postnatal nutritional conditions may damage mitochondria and suggest a mechanism that further down the road may lead to metabolic disorders and type 2 diabetes.

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