with elderly patients being more severely affected than young. There is a growing awareness concerning the health-related quality of life (QoL) in surviving ICU patients due to the gradually increasing high costs of modern ICU care, but also to the increasing body of knowledge regarding the impact of impaired muscle function on the prolonged and more complicated weaning from mechanical or assisted ventilation, extensive rehabilitation and decreased patient QoL with consequence for long-term outcomes. Specific interest is focused on underlying mechanisms, muscle type specific differences, effects of aging and the impact of specific intervention strategies.

Keywords: Myosin, Protein degradation, Muscle disease

O7.3 Neuromuscular disease, Sun 09:45–10:00

Search for causative mutations in the Austrian malignant hyperthermia (MH) population

Weigl Lukas, Mann Anda, Mashaghi Maryam, Kraft Birgit, Michalek-Sauberer Andrea

Clinical Department of Special Anaesthesia and Paintherapy, Medical University Vienna, Austria

Aim of the study: To offer a genetic test to members of Austrian families with a known malignant hyperthermia (MH) history, we analyzed the genomic DNA of 105 members of such families which were diagnosed susceptible for MH (MHS) in the in vitro contracture test for the presence of one of 31 approved causative MH mutations. In addition, for four individuals who did not show a known mutation, the complete coding region of the RYR1 was sequenced.
Methods: Of the ryanodine receptor 1 gene (RYR1) 21 exons and of the dihydropyridine receptor gene (CACNA1S) one exon were amplified with the PCR technique and sequenced. The analyzed regions thus comprised the three MH hot spot regions with 30 of the currently 31 approved MH mutations (97 %) and 74 of those 187 variants (40 %) which are listed in the European MH group register to have a possible linkage to MH. Complete sequencing of the RYR1 was done by mRNA isolation of cultured myotubes and synthesis of cDNA. Functional testing of new variants was done with Ca^{2+} release experiments with cultured myotubes using the specific RYR1 activators caffeine and 4-chloro-m-cresol (4-CmC).
Results: In only six individuals out of the 105 tested (5.7 %), we found one of the known causative mutations and in 11 individuals a possible mutation was detected (10.5 %). In three out of four individuals with the complete RYR1 sequence checked, we found new variants, which are highly suspicious of being causative for MH. These three new variants showed increased sensitivity of Ca^{2+} release against caffeine, 4-chloro-m-cresol and halothane in Ca^{2+} release experiments of cultured and differentiated skeletal muscle cells.
Conclusion: The search for approved causative MH mutations in the three hot spot regions revealed a surprising low frequency of known variants. For a genetic test of MH the list of causative mutations has to be expanded and the sequencing must not be restricted to the hot spot regions of the RYR1 gene. Supported by FWF P24922-B13 and by the Verein FWFAS

Keywords: Malignant hyperthermia, Ryanodine receptor, Calcium release

O7.4 Neuromuscular disease, Sun 10:00–10:15

Involvement of adiponectin in the pathogenesis of dystrophinopathies

Abou-Samra Michel[1]*, Schakman Olivier[2], Lecompte Sophie[1], Boursereau Raphael[1], Noel Laurence[1], Many Marie C[1], Guiot Yves[1], Gailly Philippe[2], Brichard Sonia M[1]**

*****Candidate for Young Investigator Award**

[1]Institute of Experimental and Clinical Research – UCL, London, UK; [2]Institute Of NeuroScience – UCL, London, UK

The hormone adiponectin (ApN) is decreased in the metabolic syndrome, where it plays a key pathogenetic role. We have previously shown that ApN exerts anti-inflammatory effects on the skeletal muscle in mice exposed to acute inflammation (lipopolysaccharide injection) or metabolic stress (obesogenic diet). Here we investigate whether ApN could be sufficiently potent to counteract a severe degenerative muscular disease. To this end, mdx mice (a model of Duchenne muscular dystrophy, where inflammation worsens the consequences of the genetic deficiency) were crossed with transgenic mice overexpressing ApN in order to generate mdx-ApN mice. Circulating ApN was markedly reduced in mdx mice compared to controls. Replenishment of ApN drastically reduced inflammation and oxidative stress in muscles of mdx-ApN mice and enhanced the expression of myogenic differentiation markers. Moreover, mdx-ApN mice exhibited higher global muscle force and endurance along with decreased muscle damage as quantified by curtailed extravasation of Evans Blue Dye in myofibers. Lastly, the anti-inflammatory effects of ApN were also reproduced in human myotubes in vitro. Adiponectin turns out to be an extremely potent anti-inflammatory hormone that protects the skeletal muscle against injury. These properties of ApN may be of interest in myopathies, but also in several other diseases where inflammation plays a triggering or worsening pathogenic role.

Keywords: Skeletal muscle, Inflammation, Adiponectin

O7.5 Neuromuscular disease, Sun 10:50–11:05

Characterization of a Kbtbd13-deficient mouse model that recapitulates nemaline myopathy with mutations in the KBTBD13 gene

De Winter Josine[1]*, Joureau Barbara[1], Stienen Ger JM[2], Granzier Henk[3], Ottenheijm Coen AC[4]**

*****Candidate for Young Investigator Award**

[1]Department of Physiology, VU University Medical Center, Amsterdam, The Netherlands; [2]Department of Physics and Astronomy, VU University, Amsterdam, The Netherlands; [3]Department of Physiology, Tuscon AZ, USA; [4]Department of Physiology, VU University Medical Center, Amsterdam, The Netherlands; Department of Physiology, Tucson AZ, USA

Nemaline myopathy (NM) is the most common non-dystrophic congenital myopathy and is characterized by muscle weakness and the presence of nemaline bodies in the muscle fibers. To date, nine genes are implicated in NM, of which most are associated with thin filament proteins. Recently a novel implicated gene was discovered—KBTBD13—of which the function of its protein product is unknown. NM patients with KBTBD13 mutations have muscle weakness and show a typical slowness of movement. Here, we generated a mouse model that lacks the kbtbd13 gene to obtain insight into the role of this new gene and its protein product and to elucidate the pathophysiology of this new form of NM. Methods Kbtbd13-KO mice were generated at the GEMM Core facility of the University of Arizona (Tucson, AZ,