potentials and twitch force were measured in muscle strips obtained from patients and controls. Of the 36 patients, 25 presented with chronic muscle weakness of varying degrees, up to wheelchair-dependence. The weakness was associated with intracellular Na^+ overload and edema. Older patients revealed a vacuolar myopathy or a progressive muscular dystrophy. Weakness, intracellular Na^+ overload and edema were increased and further raised by cooling and glucose/insulin, and almost completely normalized by 4 weeks of treatment with the carbonic anhydrase inhibitor acetazolamide (Jurkat-Rott et al., 2009). In vitro, the chronic weakness correlated to membrane depolarization, and acetazolamide repolarized the membrane and restored force. We conclude that membrane depolarization associated with intracellular Na^+ overload and edema causes both episodic and permanent muscle weakness. The chronic weakness is reversible in muscles which show mild or only moderate fatty degeneration. Acetazolamide has direct and beneficial effects on weak muscle and can markedly improve both forms of weakness.

In addition, we tested whether the edema in Duchenne muscular dystrophy (DMD) is caused by an osmotic effect due to increased myoplasmic Na^+ content or by inflammation. The muscle edema was quantified on STIR images using background noise as reference. Na^+ was quantified by a muscular tissue sodium concentration (TSC) sequence. A novel inversion-recovery (IR) sequence allowed us to determine mainly the myoplasmic Na^+ by suppression of the extracellular 23Na signal, e.g. from vasogenic edema. Both intracellular TSC and water content were markedly increased in DMD compared to volunteers ($p < 0.001$). We conclude that the elevated myoplasmic Na^+ concentration in DMD is osmotically relevant and causes a mainly intracellular muscle edema that contributes to the pathogenesis of DMD.

We hypothesize that antiedematous treatment can reverse the edema and prevent the edema-induced muscle degeneration.

I-11
News in non dystrophic myotonias

F. Deymeer

Not arrived

I-12
Timothy Syndrome and Cardiomyopathy

R. Bloise

Not arrived

I-13
Muscle ryanodine receptor in congenital myopathies and channelopathies

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Central core disease (CCD) and malignant hyperthermia (MH) have been linked to point mutations in the gene encoding the skeletal muscle sarcoplasmic reticulum calcium release channel (ryanodine receptor), which is localized on human chromosome 19 (RYR11). Central core disease is a relatively mild, slowly progressive autosomal dominant myopathy, characterized histologically by the presence of centrally located cores running the length of the muscle fibres. MH is a pharmacogenetic induced hypermetabolic disease. CCD linked RyR1 mutations are associated with depletion of thapsigarin-sensitive stores and to an increase of the resting calcium level. Influx of $Ca2^+$ from the extracellular environment is a major factor influencing the level of the resting intracellular [$Ca2^+$]. Our working hypothesis is that decrease of sarco(endo)plasmic reticulum $Ca2^+$ load via leaky ryanodine receptor channels and/or alteration of calcium influx via store operated channels or excitation-coupled $Ca2^+$ entry (ECCE), may account for, at least in part, the phenotype of patients with CCD, including muscle weakness and abnormal secretion of inflammatory cytokines from muscle cells. We set out to test the validity of our hypothesis by directly investigating the mechanisms activating calcium influx in myotubes from normal individuals and from patients with CCD and MH by TIRF microscopy. Our data shows that some mutations in RYR1 affect ECCE in human myotubes from CCD and MH patients; this enhanced $Ca2^+$ entry is accompanied by the generation of reactive nitrogen species and enhanced nuclear localization of NFATc1, which in turn may be responsible for the increased IL-6 released by myotubes from patients with central core disease.

I-14
Molecular pathomechanism of DM2/PROMM: similarities and differences between DM1 and DM2

G. Meola

Not arrived