In Vivo Myocardial Calcium Influx is Increased in the Delta-sarcoglycan Deficient Mouse Model of Muscular Dystrophy Cardiomyopathy. Role Of The L-Type Calcium Channel.

Introduction

- Elevated intracellular calcium levels are thought to be involved in the pathophysiology of muscular dystrophy cardiomyopathy. It is not clear whether this calcium increase is due to ion channel defects or sarcolemmal injury.
- Manganese enhanced MRI (MEMRI) can be used to assess in vivo myocardial calcium influx. Mn²⁺ enters the cardiomyocyte through the L-Type calcium channel (and other potential routes of calcium entry) and acts as a contrast agent on T1 weighted images.
- We used MEMRI to investigate myocardial calcium influx in the delta-sarcoglycan deficient mouse (Sgcd-/-) a model for Limb Girdle Muscular Dystrophy 2F and the mdx mouse a model for Duchenne Muscular Dystrophy.
- We investigated the effects of L- and T-type calcium channel blockers on MEMRI.

Results

- MEMRI was performed on 24 week old mdx and C57/B10 (WT) and 16 week old Sgcd-/- mice.
- Manganese Chloride (100µmol/g body weight) was infused through the tail vein and myocardial contrast enhancement was measured at 5 minute intervals from baseline.
- Further groups of mice were injected intraperitoneally 30 minutes prior to manganese infusion as follows:
  - All strains, 5mg/kg of the L-Type calcium channel blocker diltiazem
  - Sgcd-/- only, 10mg/kg diltiazem (following on from results of above).
  - All strains, 7.5mg/kg of the T-type calcium channel blocker mibebradil
- Mice were injected with Evans Blue Dye and uptake was scored histologically on a scale of 0 to 6.
- qRT-PCR was performed to assess expression of the pore forming subunits of the T and L-type calcium channels (CACNA1G, CACNA1H and CACNA1A).

Conclusions

- Sgcd-/- and mdx mice have increased myocardial contrast enhancement following MEMRI when compared to WT controls.
- L-type calcium channel blockade reduces myocardial calcium influx and heart rate in both WT and mdx mice whereas Sgcd-/- mice are relatively resistant to such pharmacological intervention.
- Mdx mice display significantly increased sarcolemmal injury whereas in Sgcd-/- mice it is borderline increased.
- Increased signal on MEMRI is associated with higher levels of sarcolemmal injury, although whereas MEMRI signal is relatively homogenous as a contrast agent on T1 weighted images by Evans blue dye is regional. This suggests that these are different phenomena which independently correlate with the degree of cardiac pathology in these models.

The data show there are likely to be distinct mechanisms of calcium influx in muscular dystrophy related cardiomyopathy and so treatment strategies may need to be tailored to underlying mechanisms and genotypes.

References

Manganese-Enhanced MRI of Mouse Heart During Changes in Inotropy. Hu T.C.-C., Pautier G.P., MacGowan G.A., Koretsky A.P.

Acknowledgements

University animal care staff