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Title : RIGID vs NON RIGID MH, STUDIES OF Ca^{2+} UPTAKE AND ACTOMYOSIN ATPase

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INTRODUCTION: Malignant hyperthermia(MH) has been described with two basically different clinical manifestations;patients with rigidity(R)and those without rigidity(NR). The clinical,biochemical and physiologic abberations other than rigidity are similar for both types and to date no adequate explanation has been proposed to explain the difference between them.

METHODS: From previous pilot studies[1] we have found that in patients susceptible to MH there is a significant reduction of Ca^{2+} uptake by the sarcoplasmic reticulum(SR). During the past three years we have studied muscle biopsies from 104 patients from 24 states. The samples were quick frozen in liquid N_2 and transported in dry ice to our laboratory. They were stored for up to three months at -79°C without loss in activity. We studied the Ca^{2+}uptake rate in the presence of oxalate[2],histochemical fiber typing,and actomyosin ATPase activity(AM ATPase)[3] in serially cut cryostat sections. In the study group were: patients with clinical MH:28(15R 13NR);family members of patients with MH:41; normal controls:22;and patients with other myopathies:12. Biopsies were taken using either general or local anesthesia from the vastus lateralis muscle. Age ranged from 3-81 years. Informed consent was obtained from the controls who were undergoing orthopedic surgical proceedures. Caffiene contracture studies were performed on 5 patients with MH biopsied in our hospital, and on 5 controls.

RESULTS: The Ca^{2+} uptake and AM ATPase results are summarized in this table.

Group	Ca^{2+}Uptake μM Ca^{45}/gm	AM ATPase μM Pi/gm
R MH	5.45±.38(3.5-8.7)*	0.08±.01(.01-.12)*
NR MH	3.90±.26(2.4-5.0)*#	0.14±.01(.11-.18)#
MHS Relatives	4.54±.42(3.0-7.2)*	0.11±.20(.06-.13)
Controls,Non MHS Relatives	9.94±.37(8.5-16)	0.13±.01(.12-.16)
Myopathy	8.65±.35(7.7-9.8)	0.12±.15(.09-.16)

Mean± S.E. (range)

*sig. diff. from control $p<0.05$
#sig. diff. from R MH $p<0.05$

There is a significant reduction in the SR Ca^{2+}uptake in all subjects who are susceptible to MH. Crossover occurred in 1 and 2 rigid patients compared to normals and myopathies.There was none in the NR MH group. All patients susceptible to MH showed a decreased sensitivity to caffiene(0.5-1.0mM) compared to controls(2.0-4.0mM)

DISCUSSION: Our data shows three distinctly different groups:1.Normal Ca^{2+}uptake and normal AM ATPase(controls,non MHS family members,myopathies);2.Low Ca^{2+}uptake and normal AM ATPase(NR MH);3. Low Ca^{2+}uptake and low AM ATPase(R MH). The significance of the difference of the R and NR MH groups and the relationship of Ca^{2+}uptake of SR and AM ATPase is not clear. It would be attractive to speculate that the explanation for the presence or absence of rigidity is related to the activity of AM ATPase however the correlation between the two may not be causative of the clinical difference between the R and NR types but only secondary to another defect. The two pieces of data concern two different aspects of muscle function,namely the contraction and relaxation cycles. The site of the exact defect in either form of MH is only speculative at present. From our data and from others[4]we know in both,that SR function is depressed but interplay between the contractile elements and SR has been suggested and not ruled in or out[4]. Differences in Ca^{2+} released or sequestered by the SR or a defect in the sarcolemma has not been defined. Also Ca^{2+} sensitivity of the AM ATPase in MH (known to be a function of intracellular Ca concentration) has not been studied. If there is a defect in one of these areas then the correlation between Ca^{2+}uptake and AM ATPase may be very important in understanding the differences between the rigid and non rigid forms of this syndrome

CONCLUSIONS:1.Patients who are susceptible to MH have reduced Ca^{2+} uptake into SR. In the Rigid form this is coupled with reduced AM ATPase which is normal in Non Rigid patients.2.SR Ca^{2+}uptake correlates well with caffiene contracture threshold.

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