TITLE: MALIGNANT HYPERTHERMIA SUSCEPTIBILITY(MHS): HORMONE SENSITIVE LIPASE SUGGESTED AS A CANDIDATE GENE

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The recent subregional localization of MHS to chromosome 19q12-13.2(1) can be used to suggest or eliminate candidate genes as the site for the primary defect in this disorder. We report here preliminary studies supporting a hormone sensitive lipase (LIPE) as a candidate gene in MHS.

METHODS: mRNA was purified from skeletal muscle from normal and MHS patients. Northern blots using 5 mcgm of mRNA were hybridized to 32P labeled rat LIPE cDNA (2). DNA was isolated from the blood of MHS and normal family members, and digested with 18 restriction enzymes. Southern blots using this DNA were hybridized to 32P labeled rat LIPE cDNA to evaluate linkage. MHS was confirmed by clinical history, or a skeletal muscle contracture response to halothane in vitro(3).

RESULTS: Northern blots hybridized with the rat LIPE cDNA identify a single 3.3 kB mRNA. The LIPE cDNA recognizes a Xba I and Bgl II restriction fragment length polymorphism (RFLP) which are closely linked to MHS.

Discussion: Skeletal muscle lipid metabolism appears abnormal in MHS. The source of abnormally elevated free fatty acids (FFA) in MHS appears to be triglycerides(4). Elevated skeletal muscle FFA in MHS may explain the increased release and decrease uptake of Ca++ by the sarcoplasmic reticulum, as well as the disruption of the cellular membranes and oxidative metabolism during a MH crisis. LIPE serves a crucial role in mobilizing free fatty acids (FFA) from stored triglycerides(2). Mapping data localize LIPE to 19q13.1, closely clustered with MHS(1) along with CYP2A(5) between the D19S9 and APOC2 chromosomal markers. Our northern analyses indicate that LIPE is expressed in human skeletal muscle. Linkage analyses in several extended pedigrees show no recombinants between MHS and LIPE. These results support the notion that LIPE should be carefully studied to evaluate if it harbors a mutation which explains MHS.

References:
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TITLE: BRAIN BIOENERGETICS DURING CARDIOPULMONARY RESUSCITATION

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A major source of controversy in cardiopulmonary resuscitation (CPR) centers around the effect of systemic acidemia on brain function. We evaluated the effect of progressive systemic acidemia during CPR on brain bioenergetics using phosphorus magnetic resonance spectroscopy (^{31}P-MRS) to directly measure brain pH and ATP concentration with 1 min resolution.

Methods: Six mongrel dogs (15-18 kg) were anesthetized with pentobarbital (10 mg/kg, iv) and fentanyl (20 ug/kg, iv). Catheters were placed for arterial and sagittal sinus pressure measurement, blood gas sampling and radiolabeled microsphere injections for cerebral blood flow measurements. The trachea was intubated and an inflatable vest placed around the thorax for CPR. CPR was begun after 6 mins of ventricular fibrillation (vf). Cerebral perfusion pressure was maintained greater than 60 mmHg by continuously administering epinephrine (10 ug/kg/min) and adjusting the vest pressure. Intracellular bicarbonate was calculated using ^{31}P-MRS measurements of brain pH, assuming brain CO_2 equal to sagittal sinus CO_2, and applying the Henderson-Hasselbach equation.

Results: After 6 mins of vf, brain pH dropped to 6.29 ± .09 (mean ± SEM) and brain ATP was totally depleted. After 6 mins of CPR, ATP was 86% ± 6.8 of control. Bicarbonate values in table are expressed as meq/L change from the animal's own control. Analysis of variance and two tailed paired student's t-test were applied to arterial versus brain bicarbonate.

	Control	6 min CPR	12 min CPR	35 min CPR
CBF	35±4	68±14	57±22	33±9
ΔArt. Bicarb	0	-6.5±1.4	-9.1±1.6	-11.1±0.8
ΔBrain Bicarb	0	-12.5±1.3	-10.6±1.6	-2.7±1.4
P-value	-	.001	.135	.001
Arterial pH	7.41±.08	7.29±.04	7.22±.05	7.10±.04
Brain pH	7.11±.02	6.61±.07	6.88±.03	7.03±.03

Discussion: Despite using a short period of no brain perfusion (6 min), severe bioenergetic failure was demonstrated by low brain pH and absent ATP. However, after 6 min of CPR, ATP had recovered. At 35 min of CPR, brain bicarbonate was not significantly different (p = .12) from pre-arrest despite severe ongoing systemic metabolic acidemia. Brain bicarbonate recovery was as rapid as that seen after intracranial hypertension without severe systemic acidemia. We conclude that brain pH is protected against systemic acidosis during prolonged CPR when CPR is effective in generating pre-arrest levels of CBF.