Anesthesiology
V 75, No 3A, Sep 1991

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EXCESSIVE ACYLATION OF TRIGLYCERIDES IN MUSCLE FROM SWINE EXHIBITING CLINICAL MALIGNANT HYPERTHERMIA (MH): EVIDENCE FOR HETEROGENEITY IN THE PATHOGENESIS OF MH.

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It was previously demonstrated that MH susceptible swine (by breeding, barnyard challenge and diagnostic testing) with reduced triglyceride levels and free fatty acids (FFAs) in skeletal muscle could not exhibit an *in vivo* episode of MH and had a normal threshold of Ca^{2+}-induced Ca^{2+} release (TCICR) as determined with heavy sarcoplasmic reticulum fractions (HSRFs).[1] The present study examines triglycerides and FFAs in the muscle of the same strain (Yorkshire/Duroc cross) of swine at a time that they exhibited clinical episodes of MH to determine if any aspect of lipid metabolism correlates with the potential to exhibit an MH episode. **METHODS**. Swine (4 MH+, 4 MH-) were challenged *in vivo* with halothane and succinylcholine to elicit an MH episode.[1] The TCICR was determined in HSRFs using arsenazo III and pyrophosphate, as previously described.[1] Triglycerides and FFAs were determined by gas chromatography.[1] **RESULTS**. All 4 MH+ swine exhibited unequivocal signs of MH (rigidity, hyperthermia, acidosis, tachycardia) when challenged with halothane and succinylcholine. The TCICR in muscle (longissimus dorsi) removed immediately prior to *in vivo* challenge was significantly ($P<.05$) lower in HSRFs from the MH+ swine (5.2 ± 1.1 µmol Ca^{2+}/mg protein; mean±SEM) than in those from the MH- swine (9.2 ± 1.1). Incubates of skeletal muscle also removed before *in vivo* challenge exhibited a decrease in triglyceride fatty ester levels in MH- swine in the present study (-1063 ± 1550 pmol $mg^{-1}hr^{-1}$; mean ± SEM) and in the MH+ swine unable to exhibit an *in vivo* episode of MH in the previous study (-580 ± 1000). In contrast, the triglyceride fatty ester levels in incubates of muscle from the MH+ swine *increased* in the present study ($+5215\pm2128$; $P<.05$) relative to contemporary controls *and these swine elicited an MH episode*. The composition of the newly synthesized triglyceride suggested that the fatty esters were derived from the acylCoA pool, not from phospholipids or *de novo* synthesis of FFAs. **DISCUSSION**. In MH susceptible swine in the Yorkshire/Duroc strain the acylation of acylCoAs to triglycerides upon homogenization and incubation of the muscle correlated with ability to express an MH episode and the low TCICR (Table). AcylCoAs are the activated form of FFAs and when they are readily available would be expected to enhance Ca^{2+} release, as reported for fatty acids.[1] This is the first biochemical explanation of why an MH episode does not always occur in swine carrying the defect. That is, acylCoAs, which depend on the metabolic state of the subject, must be available to elicit an MH episode. This acylCoA defect in the Yorkshire/Duroc strain appears to be a different lipid defect from the elevated FFAs observed in the British Landrace swine[2] and in humans,[3] but either defect can elicit an MH episode.

References: 1. Biochem Cell Biol 68 1195, 1990; 2. Biochim Biophys Acta 638 40, 1981; 3. Br J Anaesth 58 1433, 1986

Table. Requirement for elevated acylCoAs in MH.

Genetics	Triglyceride acylation	Contracture test	*In vivo* challenge	TCICR
MH-	-	-	-	normal
MH+ ref#1	-	+	-	normal
MH+	+	+	+	reduced

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TITLE: KETAMINE EFFECTIVELY REDUCED MYOGLOBINEMIA INDUCED BY SUCCINYLCHOLINE

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As we have shown in the previous report, succinylcholine (Sch) produced high serum myoglobin and CK levels during halothane anesthesia in children (1) and thiamylal 4 mg/kg was effective to suppress the increase of both levels in children (2). The present study was designed to examine the effect of ketamine on changes in serum myoglobin and CK levels in adults, and compared with the effect of thiamylal.

Seventy five patients aged from fourteen to thirty-nine, scheduled for minor surgical procedure were subjected to this study (with informed consent and approvals by the ethical committees of the hospitals). They were divided into three groups; In the first group Sch 1 mg/kg was administered to facilitate tracheal intubation (group O) after induction with N_2O, O_2 and halothane using a mask. In the rest of two groups thiamylal 4 mg/kg (group T) or ketamine 2 mg/kg (group K) was injected for an intravenous induction prior to the administration of Sch 1 mg/kg. Anesthesia was maintained with N_2O, O_2 and halothane in all three groups. Blood samples were taken before and 5, 20, 60 min after the injection of Sch. Statistical analyses were carried out using ANOVA and either paired or non-paired Student's t-test.

Results; After the Sch administration myoglobin and CK values increased in all three groups. There was marked increase in group O compared with group T and group K, and no significant difference was observed between group T and group K. The tables show the values of myoglobin (Table 1) and CK (Table 2).

It is suggested that the injection of thiamylal effectively suppressed the increases in serum myoglobin and CK in adults as well as in children. Ketamine 2 mg/kg is also shown to have suppressive effects on increases in both values for the frist time. Further studies are necessary to clarify the mechanism of suppression, and whether the mechanism is same in both drugs or not is not clear from the present study.

Myoglobin Value (ng/ml, mean±SD)

Group(n)	before	5 min	20 min	60 min
O (31)	33 ± 15	957 ±1363	1720 ± 2521	2293 ± 3312
T (21)	43 ± 36	80 ± 72	129 ± 146	161 ± 151
K (23)	36 ± 31	91 ± 148	128 ± 217	143 ± 144

CK Value (IU/l, mean±SD)

Group(n)	before	5 min	20 min	60 min
O (31)	52.9±20.1	69.3±54.3	105.2±119.0	206.5±249.5
T (21)	66.0±66.1	66.5±66.8	63.0± 53.7	75.5± 59.9
K (23)	56.9±29.7	56.6±30.7	54.3± 28.9	62.5± 33.1

Reference 1. Masui, 37:421-427, 1988
2. Anesthesiology, A1045, 1989