

Title : MH MUSCLE: EFFECT OF NEUROTRANSMITTERS OR \uparrow TEMPERATURE

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Introduction: Prior reports are contradictory about the roles of the somatic and sympathetic nervous systems in porcine malignant hyperthermia (MH): epidural block prevented halothane-induced muscle rigidity,¹ and α -sympathetic agonists triggered MH,² but total spinal block (and sympathetic denervation) did not prevent halothane-induced MH.³ The present study evaluates effects of cholinergic and sympathetic agonists, and hyperthermia, upon isolated perfused porcine skeletal muscle.

Method: During thiopental- N_2O anesthesia susceptible and normal Poland China swine were completely transected at the L₁-L₂ level and the remaining caudal body was perfused with a roller pump-oxygenator, thus isolating the muscle of the hams, flanks, and legs from the effects of the spinal cord and sympathetic nerves. Oxygen consumption ($\dot{V}O_2$), assumed to represent only muscle, was calculated from the Fick relationship (flow \times arteriovenous oxygen content difference). Blood lactate estimated glycolytic metabolism. Protocols were 1) carbachol (10⁻⁴M), isoproterenol (continuous infusion at 2.5 μ g/kg total caudal weight/min and decreased to 1.2 μ g/kg/min after 12 min) or neosynephrine (0.2-25 μ g/kg/min) were added to the perfusate to mimic cholinergic and sympathetic influences; 2) in the absence of drugs, incremental surface and perfusate warming to 43°C (deep muscle temperature) assessed the effects of hyperthermia per se upon the metabolism of skeletal muscle.

Results: 1) Carbachol increased $\dot{V}O_2$ from 7 to 18 ml O_2 /min/kg muscle weight (determined by dissection) in susceptible muscle, but did not significantly increase $\dot{V}O_2$ of normal muscle. Likewise, carbachol increased blood lactate from 4 to 13 μ mol/ml in susceptible muscle without affecting that of normal muscle. β -stimulation decreased susceptible and normal muscle $\dot{V}O_2$ slightly, about 1 ml O_2 /min/kg, and increased blood lactate progressively and similarly in both types of muscle. α -stimulation did not alter aerobic or anerobic metabolism, had similar effects on blood pressure (dose-response curves), and produced similar tissue edema in susceptible and normal muscle. 2) Progressive hyperthermia gradually increased $\dot{V}O_2$ (Q_{10} effect) and decreased lactate to similar degrees in susceptible and normal muscle until 41°C. Above 41°C, susceptible muscle $\dot{V}O_2$ and lactate rapidly increased to 18 ml O_2 /min/kg and 17 μ mol/ml, respectively; normal muscle $\dot{V}O_2$ and lactate were markedly (significantly) lower. Thus either carbachol or hyperthermia triggered metabolic and acid-base changes typical of MH in the absence of triggering anesthetic agents.

Discussion: Carbachol is well accepted as a laboratory equivalent of acetylcholine and these results strongly suggest that skeletal muscle of stress susceptible swine has abnormal inherent responses to cholinergic drugs or chemical depolarizers including acetylcholine, and to increased temperature. While normal swine should tolerate increased muscle activation secondary to exercise or excitement, or succinylcholine, the susceptible swine would be expected to increase aerobic and anerobic metabolism abnormally, with an associated metabolic and respiratory acidosis. These changes would be augmented by the effects of sympathetic mediated β -stimulation, which would add to the metabolic and acid-base stresses of cholinergic activation. Thus, while β -stimulation of glycolysis is similar in normal and susceptible swine, the consequences are greater in the latter. These data do not examine function of the somatic or autonomic nervous systems. These systems may be abnormal, but it is not essential for them to be so to explain triggering of MH. We conclude 1) that somatic motor nerves can trigger metabolic and acid-base changes typical of MH in the absence of anesthetic agents via abnormal responses of susceptible muscle to cholinergic stimulators, 2) that the sympathetic nervous system augments these changes via normal adrenergic mechanisms and responses, and 3) that increased temperature can be an aggravating factor.

References:

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