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COMMENTARY

MALIGNANT HYPERTHERMIA

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Malignant hyperthermia (MH) is a disastrous metabolic syndrome which occurs in certain patients exposed to the volatile anesthetics and/or non-depolarizing muscle relaxants [1]. It is a pharmacogenetic disorder that appears to be inherited in an autosomal dominant fashion [2]. The syndrome as originally described is characterized by tachycardia, arrhythmias, fever and rigidity [3]. This progresses to death unless it is rapidly recognized and effectively treated. An effective treatment for this syndrome is available—it involves immediate recognition, removal of the triggering drugs, cooling of the patient, and infusion of sodium dantrolene [4]. The basic abnormality of this disorder is believed to reside in skeletal muscle since 70% of susceptible patients have elevated resting serum creatine kinase (CK) activity, indicating an underlying myopathic process [1]. Furthermore, during an MH crisis, serum CK activity increases remarkably as does serum K^+ reflecting ongoing muscle destruction during the exposure to the triggering drugs. Other clinical evidence of a muscle abnormality is the marked rigidity that occurs in the MH patient during an acute episode. Rigidity is often observed even in the presence of an adequate amount of non-depolarizing muscle relaxants [4]. This suggests that muscle activation is occurring despite apparent blockade of the neuromuscular junction. Increased sensitivity of the excised muscle to caffeine has also suggested an abnormality of skeletal muscle [5]. It has been shown that excised muscles from patients who have previously experienced MH episodes develop contracture to caffeine at a much lower concentration of caffeine than does normal muscle [5, 6]. Caffeine is known to cause release of calcium from the intracellular Ca^{2+} storage sites in skeletal muscle [7]. The increased sensitivity of MH muscle to caffeine has been utilized as a diagnostic test to distinguish between normal and MH muscle [8]. The sensitivity to caffeine along with the prominent clinical manifestation of rigidity has pointed to an abnormality of the muscle sarcoplasmic reticulum (SR). The SR is that organelle in the muscle cell which controls the availability of Ca^{2+} during contraction and relaxation and is the major site of action of caffeine.

Investigations of SR from MH muscle have resulted in conflicting data. Three experimental methods have been used to study SR function, and each has resulted in a different conclusion [9–13]. Interpretation of these investigations into SR function has been hampered by the fact that those patients termed MH have often been defined as susceptible to MH by the caffeine contracture test. However, sensitivity to caffeine is not necessarily synonymous with the MH syndrome itself. Gronert [1] has set out distinct criteria for defining those patients who have had genuine episodes of MH. It is important that any further investigations into the pathophysiology of MH require delineation of the defined criteria for MH for each patient from whom a muscle specimen is obtained. Whether one should also categorize the patient by caffeine contracture testing as well is debatable.

To return to consideration of available studies of SR function, three methodologies have been used: (1) isolated SR [9–11]; (2) skinned muscle fibers [12]; and (3) cryostat thin sections of muscle samples [13]. The first area of study, the isolated SR, has itself resulted in conflicting reports of either decreased function, slight activation of uptake, or no alterations of uptake. This variability can be attributed to at least two important factors: (1) differing methods of isolation, differing purity and differing assay conditions; and (2) human muscle is made up of several fiber types, which vary from patient to patient and also from muscle to muscle [14]. Each fiber type has a characteristic SR with variable rate and capacity of calcium uptake [15, 16]. When a piece of muscle is homogenized, the SR fraction obtained is derived from different fibers, and any distinct alteration in calcium transport in a particular fiber type would be obscured by the homogenization.

Skinned fiber examination of SR function involves a less complex physiologic system than cut muscle fibers; thus far, only one group has studied skinned fibers from MH muscle and that group has not fiber typed their specimens. The preparation of a skinned fiber involves the immersion of the excised muscle in a buffer solution containing ethylene glycol bis (beta-aminoethyl ether)-*N,N,N*^{1},*N*^{1}-tetracetic acid disodium (EGTA) which dissolves part of the sarcolemma, allowing the unencumbered exchange of small molecules between the medium and the environment surrounding the SR and myofibrils [17]. The muscle is then dissected into individual fibers and a fiber is placed on a strain gauge to measure contractile activity. Calcium uptake has been measured in three ways: (1) measurement of $^{45}Ca^{2+}$ accumulation into the SR of a skinned fiber by liquid

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scintillation counting [18]; (2) estimation of Ca^{2+} accumulation by the release of Ca^{2+} with a high dose of caffeine (25–50 mM) and measurement of the contractile response of the fiber to the released Ca^{2+}; and (3) by optical measurement of the Ca^{2+}-oxalate precipitates in the SR [18]. The skinned MH fiber preparation has shown that SR from MH patients is more sensitive to caffeine, leading to Ca^{2+} release at a lower caffeine concentration [18]. Since the response to caffeine is, in part, dependent upon the concentration of calcium in the SR, the increased sensitivity to caffeine suggested that the MH SR might accumulate calcium at a greater rate than normal human SR [12, 19]. This interpretation was supported by determinations of calcium accumulation by light scattering measurements of the formation of calcium–oxalate precipitates in the cisterna of the SR vesicles. The authors demonstrated that the rate of Ca^{2+} uptake by the chemically skinned MH fibers could be decreased significantly by incubation with phosphodiesterase. Control fibers from normal human muscle were insensitive to either cAMP or phosphodiesterase which indicated to the authors an abnormality in MH muscle with respect to cAMP regulation. The observed difference might be attributed to an alteration in fiber type between MH and normal human muscle.

The cryostat thin section is an alternative and recently developed methodology for measurement of SR Ca^{2+} uptake [13]. Muscle biopsy specimens are frozen and divided into thin sections with a cryostat. Measurements of $^{45}Ca^{2+}$ uptake in thin sections of MH muscle demonstrate a decreased ability to accumulate calcium over a 30-min period. Serial sections have shown that type IIb fibers of MH muscle have decreased ability to accumulate calcium [20]. These findings obviously are in contra-distinction to those of Wood *et al.* [12], and at this time the differences are inexplicable. The possibility exists that each group was sampling different Ca^{2+} transport characteristics.

It has been assumed that a marked increase in intracellular calcium occurs during the MH crisis [1]. This assumption is based on the appearance of rigidity, the effectiveness of dantrolene in treatment, and the sensitivity of excised muscle to caffeine. However, there have been no direct measurements to prove this hypothesis. Dantrolene sodium has been shown to cause muscle relaxation at some site beyond the neuromuscular junction and has been shown *in only one study* to decrease the release of calcium from isolated skeletal muscle sarcoplasmic reticulum [21, 22]. Other studies have also demonstrated at least a role of extracellular calcium in contracture development in biopsied muscle [23, 24]. Moulds and Denborough [24] demonstrated that caffeine contracture could be prevented if MH muscle were bathed in calcium free medium. This is distinctly different from the response of normal skeletal muscle which is not as dependent on extracellular calcium. Gruener and Blanck [25] have utilized the drugs verapamil and D600, which inhibit movement of Ca^{2+} through the slow channels, to demonstrate that halothane twitch potentiation in MH muscle may involve extracellular calcium. Both of these studies strongly suggest that an abnormality of the sarcolemma may exist. Gallant and Godt [26] have, in fact, shown that halothane depolarizes porcine MH muscle and that dantrolene can reverse this depolarization. At this time it is difficult to interpret mechanistically the effects of two drugs, halothane and dantrolene, which considering their high degree of lipid solubility probably both have multiple sites of action within the muscle cell membranes.

One of the many clinical puzzlements of MH is the varied appearance of the syndrome [1, 27]. The initiation of the syndrome has been reported to occur immediately upon induction of anesthesia as well as later during the anesthetic and even afterwards in the recovery room. Often the triggering of the syndrome does not occur until a second or third exposure to the anesthetic. Certainly the combination of succinylcholine and halothane appears to be the most potent of triggering drugs. However, initiation by halothane alone is often reported to occur much later, for example 60–90 min after exposure. This suggests the possibility that muscle activation might be an important aspect in the rate of development of the syndrome. Initial depolarization and fasciculation caused by succinylcholine result in release of calcium into the myoplasm. In the presence of halothane, inhibition or activation of an MH sensitive site might result in continual and increasing calcium availability to the myofibrils and mitochondria. Little experimental evidence is currently available to support this view. It is interesting to hypothesize that a halothane (or other volatile anesthetic) induced imbalance in Ca^{2+} uptake and Ca^{2+} release will not manifest itself in an MH crisis until pushed to the maximum by the normal physiologic or pharmacologic process involving muscle activation and Ca^{2+} release. Preliminary investigations have shown the prevention of halothane-induced MH in pigs treated with 2 mg/kg of the non-depolarizing muscle relaxant metocurine iodine [28].

Another aspect of MH which has led to diagnostic and experimental uncertainty is the varied symptomatological appearance of MH. Denborough and Lovell [3] described the patient with rigidity, fever, metabolic acidosis and arrhythmias. Are we justified in including or excluding from the MH category those individuals who do not have all the clinical manifestations of MH? For example, is a patient with fever, acidosis, tachycardia, and elevated serum creatine kinase an MH patient even if he does not demonstrate rigidity? Does this patient have a related disorder and is he at risk for a subsequent lethal anesthetic triggered episode? If this patient were, in fact, termed MH and included in an experimental protocol for evaluation of SR function, variability in measurement of SR Ca^{2+} uptake could appear because this patient might have a different locus for his muscle defect.

It is presently accepted by many investigators that the caffeine contracture test will define those patients who are MH susceptible and those who are not. Yet there are no reported data of patients with an unusual anesthetic history and negative caffeine contracture test that subsequently have been challenged with the triggering drugs, halothane and succinylcholine. Great variability exists from laboratory to laboratory with respect to the particular muscle used for caffeine

contracture examination and the particular drugs used to distinguish between MH and non-MH muscle [1]. One area of controversy involves the use of halothane in combination with caffeine to amplify the contracture response. Those patients who manifest increased sensitivity to caffeine in the presence of halothane, but not to caffeine alone have also been defined as MH susceptible [2]. A number of MH investigators state that the group distinguished by the halothane–caffeine contracture are not MH susceptible. This controversial topic is considerably confused by a lack of knowledge of normal responses of human skeletal muscle to the halogenated hydrocarbon anesthetics. Furthermore, as in the mechanism of anesthesia itself, the molecular interactions of halothane with the constituents of a muscle cell are essentially unknown. Utilizing halothane in combination with caffeine in a complex system, the cut muscle, to make a definitive and life-threatening decision as to MH susceptibility is, therefore, fraught with uncertainty.

In summary, the clinical syndrome of MH has been well described and can be appropriately treated. The laboratory diagnosis and pathophysiologic mechanisms of MH are, at best, in a state of uncertainty and will probably only be clarified when more fundamental biochemical distinctions can be made between normal and MH muscle.

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