Effects of Anesthetic and Related Agents on Calcium-induced Calcium Release from Sarcoplasmic Reticulum Isolated from Rabbit Skeletal Muscle

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We have investigated the effects of anesthetic and related agents on Ca^{2+}-induced Ca^{2+} release (CICR) in heavy sarcoplasmic reticulum isolated from rabbit skeletal muscle. The purpose of this study is to elucidate their possible role as triggering agents in malignant hyperthermia (MH). None of the agents (ketamine, procaine, lidocaine, succinylcholine, pancuronium and fentanyl) affected CICR at clinical concentrations. At higher concentrations, procaine, pancuronium and succinylcholine inhibited CICR, but ketamine rather potentiated it. It is unlikely that lidocaine is a potent facilitator of CICR at any concentrations. We conclude that procaine, lidocaine, non-depolarizing muscle relaxants and opiate can be used safely for MH susceptible patients and that ketamine and succinylcholine are not recommended. (Key words: calcium-induced calcium release, sarcoplasmic reticulum, anesthetics, muscle relaxants, malignant hyperthermia)

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Malignant hyperthermia (MH) is a potentially lethal pharmacogenetic disorder triggered in genetically predisposed patients by certain anesthetic agents. It is important for the anesthetist to select the anesthesia technique least likely to trigger an adverse reaction in malignant hyperthermia susceptible (MHs) subjects. Most volatile anesthetics have been accepted as triggering agents for MH. Among other anesthetic and related agents practically used, procaine and pancuronium have been thought to be clinically safe for MHs patients while ketamine, lidocaine and succinylcholine to be dangerous[1-3]. MH triggering potential of drugs except for volatile anesthetics, however, remains controversial, partly due to the lack of available *in vitro* data. Indeed, the MH Association of U.S.A. has recently removed amide local anesthetics from the list of triggering agents[4].

It is the current consensus that MH is due to a failure to control intracellular ionized calcium (Ca^{2+}) concentration in the skeletal muscles[2,3]. Several mechanisms are considered to be involved in the regulation of calcium level. Sarcoplasmic reticulum (SR) is the major organelle to regulate Ca^{2+}. Endo and colleagues[5] proposed that MH is induced by a hereditary abnormality in Ca^{2+}-induced Ca^{2+} release (CICR) from SR. Although CICR may not be the primary

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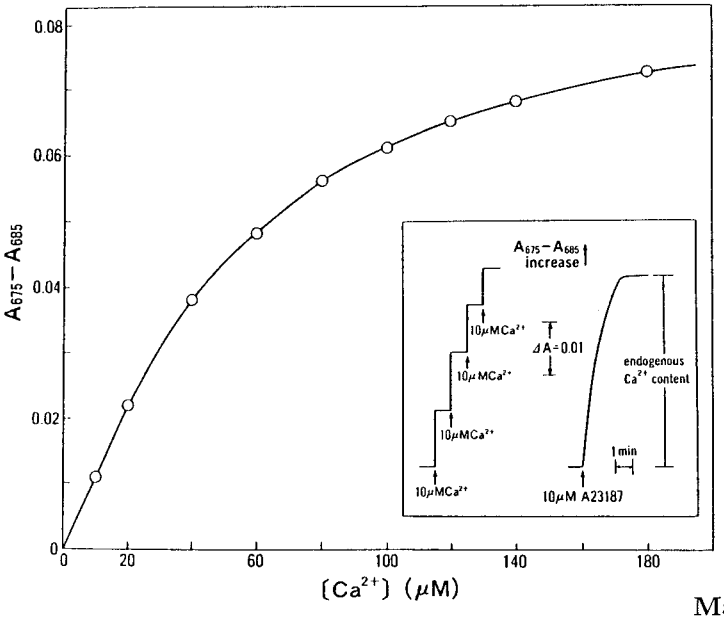

Fig. 1. The absorbance changes of arsenazo III as a function of Ca^{2+} concentration at 675–685 nm after addition of $CaCl_2$ into the measuring cuvette. Reaction mixture: 20 mM MOPS (pH 7.0) containing 0.1 M KCl, 1.5 mM $MgCl_2$, 28 μM arsenazo III and 1.5 mg protein/ml at 27°C. Inset shows the A23187 method. Endogenous Ca^{2+} content of SR was measured by adding 10 μM ionophore A23187 to the same reaction mixture as above.

mechanism of Ca^{2+} release in excitation-contraction coupling, the additional Ca^{2+} released through this mechanism in MH muscles would cause hypercontraction and an abnormal rise of the temperature. Dantrolene, a therapeutic agent for MH, has been reported to inhibit the CICR[6,7]. In contrast, volatile anesthetics such as halothane and enflurane are potentiators of the CICR and have been incriminated as causative agents[8–11]. Caffeine also facilitates CICR and is more potent in the *in vitro* contracture response in MH skeletal muscles than in normal muscles[12,13]. Caffeine-induced contracture model is useful for screening MH triggers, since anesthetics that least potentiate the contracture may not be expected to trigger MH[14]. Some false-positive results have been reported, suggesting that other mechanisms than CICR are responsible for the increased myoplasmic Ca^{2+} during caffeine-induced contracture[15–17]. It is thus postulated that effects of the drugs on CICR are more closely related to the potency to trigger MH than those on caffeine-induced contracture.

In the present study, we investigated the effects of various anesthetic and related agents on the CICR of the sarcoplasmic reticulum (SR).

Materials and Methods

Preparation of SR: White muscle from the back and hind limbs of rabbit was fractionated at 4°C by differential centrifugation. The heavy fraction of SR, which was used as SR throughout the study, was collected according to the method of Kirino and Shimizu[18]. Briefly, about 250 g of white muscle was homogenized four times (each period lasting for 20 s) in a Waring blender in five volumes of 10 mM 3-(N-morpholino) propanesulfonic acid (MOPS) (pH 7.0). The homogenate was centrifuged for 20 min at 2,800 × g, and then the supernatant was filtered through eight layers of cheese-cloth. The pellet sedimented by centrifugation of the filtrate for 40 min at 14,000 × g was resuspended in 10 mM MOPS (pH 7.0) containing 50 mM KCl. After centrifugation of the suspension for 15 min at 3,000 × g, the supernatant was spun down at 55,000 × g. The pellet, referred to as SR, was resuspended in either buffer of 5 mM MOPS (pH 7.0) containing 0.1 M KCl or of 10 mM MOPS (pH 7.0) containing 0.3 M sucrose. The SR preparation in former buffer was stored at 0°C for Ca^{2+} release experiment, which was performed within 15 hours after isolation. The SR preparation in latter buffer was stored at −80°C until use for the measurement of Ca^{2+}-ATPase activity.

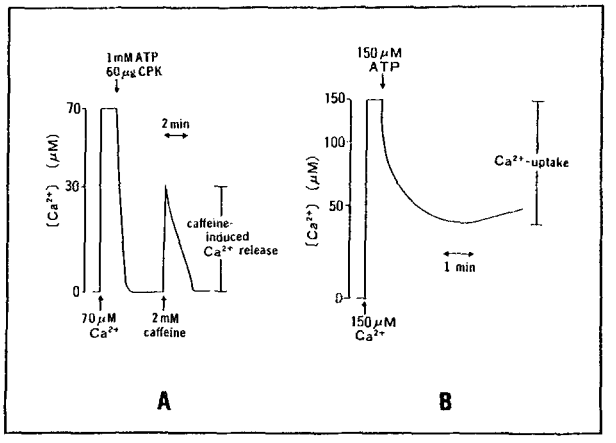

Fig. 2. (A) Caffeine-induced Ca^{2+} release from SR. Ca^{2+} preloading causes changes in absorbance moving signal upwards. Addition of ATP activates Ca^{2+} uptake by SR, reducing the absorbance signal to zero Ca^{2+} outside the SR membrane. 2 mM caffeine triggers Ca^{2+} release. Assay medium: 20 mM MOPS (pH 7.0) containing 0.1 M KCl, 1.5 mM $MgCl_2$, 28 μM arsenazo III and 1.5 mg protein/ml with an ATP-regenerating system consisting of 20 μg/ml creatine kinase and 5 mM creatine phosphate at 27°C. Total Ca^{2+} content of SR was adjusted to one-third of its maximum Ca^{2+} capacity. (B) ATP-induced Ca^{2+} uptake under blocking CICR with high Mg^{2+} concentration. At the positions indicated by arrows, 150 μM Ca^{2+} or 150 μM ATP was added. Experimental conditions: 20 mM MOPS (pH 7.0) containing 0.1 M KCl, 10 mM $MgCl_2$, 28 μM arsenazo III and 1.0 mg protein/ml at 27°C. In (A) and (B), the anesthetic and related agents were added 1 min prior to the addition of $CaCl_2$.

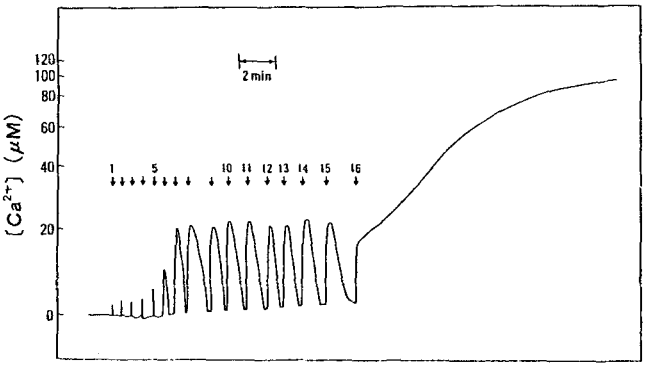

Fig. 3. Determination of the maximum storable Ca^{2+} content using CICR phenomenon. In the presence of an ATP-regenerating system, 20 μM Ca^{2+} was added sequentially to the SR suspension until CICR occurred. Numbers above the traces indicate the number of each Ca^{2+} addition. The total amount of Ca^{2+} stored before CICR represents the maximum storable Ca^{2+} content of SR. Conditions: 20 mM MOPS (pH 7.0) containing 0.1 M KCl, 1.5 mM $MgCl_2$, 0.5 mM ATP, 28 μM arsenazo III and 1.5 mg protein/ml with an ATP-regenerating system consisting of 20 μg/ml creatine kinase and 5 mM creatine phosphate. Test agents were added 1 min prior to the initial Ca^{2+} addition.

Assay: Ca^{2+} release and Ca^{2+} uptake were measured at 27°C with a metallochromic indicator method using arsenazo III[19]. Extravesicular free Ca^{2+} concentration was monitored by the difference in absorbance of 28 μM arsenazo III at 675 and 685 nm with a dual wavelength spectrophotometer (HITACHI model 356). Figure 1 shows a standard curve of Ca^{2+} concentration. Caffeine-induced Ca^{2+} release experiments were initiated by adding 1 mM ATP to the reaction mixture (3 ml) of 20 mM MOPS (pH 7.0), 0.1 M KCl, 1.5 mM $MgCl_2$, 28 μM arsenazo III and 50–80 μM $CaCl_2$ with an ATP-regenerating system consisting of 20 μg/ml creatine kinase (CK) and 5

mM creatine phosphate. When Ca^{2+} accumulation rate reached a steady state, Ca^{2+} release was triggered by the addition of 2 mM caffeine (fig. 2A). The SR protein concentration in the reaction mixture was 1.5 mg protein/ml. The Ca^{2+} content of SR in a resting muscle is generally one-third to one-fourth of its maximum Ca^{2+} capacity[20]. The amount of Ca^{2+} to be sequestered by SR is thus given from both values of the maximum storable Ca^{2+} content and of the endogenous Ca^{2+} content. The former was determined based on CICR (fig. 3) whereas the latter measured spectrophotometrically using ionophore A23187 (fig. 1). Certain amount of Ca^{2+} (50–80 μM Ca^{2+}) was added to the SR suspension so that total Ca^{2+} content of SR would be adjusted to one-third of the maximum capacity.

The ATPase activity was assayed at 27°C by measuring the amount of inorganic phosphate liberated according to Martin and Doty[21]. The time course of inorganic phosphate liberation after adding ATP was linear within 2 min and about 10% of initial ATP was hydrolysed for 1 min incubation (data not shown). Thus, in this study, the reaction was terminated by adding 5% (w/v) trichloroacetic acid after incubation for 1 min. Assay medium (1 ml) consisted of 20 mM MOPS (pH 7.0), 0.1 M KCl, 5 mM $MgCl_2$, 1 mM ATP and enzyme preparation. The SR protein concentration of the assay medium was 100 μg protein/ml. Ca^{2+}-ATPase activity is defined as the difference between the ATPase activity measured in the presence of 10 μM free Ca^{2+} and that in the presence of 1 mM EGTA. Ca^{2+}-ATPase activity is proportional to the unidirectional rate of Ca^{2+} uptake because of tight coupling between the Ca^{2+}-ATPase and Ca^{2+} transport. Thus we studied the effect of the anesthetics on the Ca^{2+} uptake activity by blocking the CICR with high Mg^{2+} concentration (fig. 2B)[22]. The reaction mixture consisted of 20 mM MOPS (pH 7.0), 0.1 M KCl, 10 mM $MgCl_2$, 28 μM arsenazo III, 150 μM $CaCl_2$, 150 μM ATP and enzyme preparation. The SR protein concentration of the reaction mixture was 1 mg protein/ml. The effect of mitochondrial contamination was negligible, since the results were not affected by adding 5 mM sodium azide.

Chemicals: Arsenazo III (contamination Ca^{2+} <0.04μmol/mg), ATP-Na_2 and procaine hydrochloride were purchased from Sigma Chemical Co. The ionophore A23187 was obtained from Calbiochem Behring Corp. Pancuronium bromide and ketamine hydrochloride were kindly supplied from Sankyo Co. Succinylcholine chloride and lidocaine hydrochloride were also obtained from Kyorin Co. and Fujisawa Pharm. Co. respectively. All other reagents used were of analytical grade.

Miscellaneous: All solutions were made with distilled-water purified to >17.5 MΩ-Cm by a MilliQ system (Millipore Corp.). Protein concentrations were determined by the method of Lowry et al.[23] using bovine serum albumin as a standard. In an EGTA-Ca^{2+} buffer system, an apparent binding constant between EGTA and Ca^{2+} was taken as $10^{6.4}$ at pH 7.0[24]. All experiments were carried out in triplicate and each of them was repeated at least 4 times. Results are means of three measurements varied by less than 10%.

Results

1) Effects of anesthetic and related agents on caffeine-induced Ca^{2+} release

None of the agents studied (ketamine, procaine, lidocaine, succinylcholine and pancuronium) influenced the caffeine-induced Ca^{2+} release from SR at their clinical concentrations, whereas at the higher concentrations they inhibited the Ca^{2+} release dose-dependently except for succinylcholine (fig. 4). As for other drugs, 100 μM of d-tubocurarine and vecuronium inhibited the caffeine-induced Ca^{2+} release by 40% and 25%, respectively. Fentanyl also suppressed the net Ca^{2+} release by 20% at 1 μM.

2) Effects of anesthetic and related agents on Ca^{2+}-ATPase activity

As shown in figure 5, no significant alteration in ATPase activity was observed for all drugs tested at their clinical concentrations. At the higher concentrations, however,

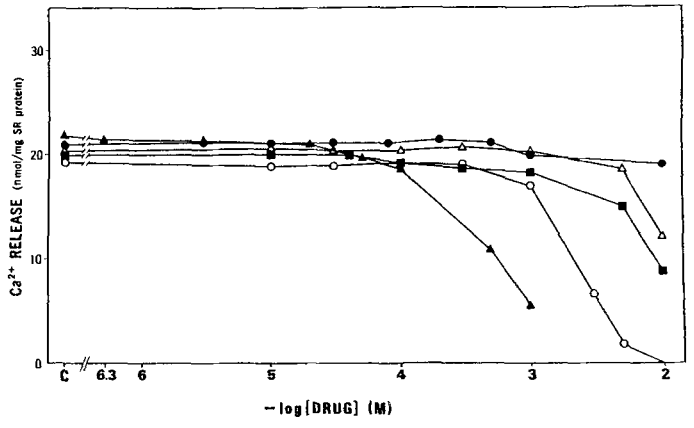

Fig. 4. Effects of the anesthetic and related agents on the caffeine-induced Ca^{2+} release. Conditions are the same as in figure 2A. Drugs were (■) ketamine, (○) procaine, (△) lidocaine, (●) succinylcholine and (▲) pancuronium. C indicates the value before the addition of the test drugs. The Ca^{2+} release in ordinate indicates net Ca^{2+} release, which is determined by the balance of Ca^{2+} efflux and Ca^{2+} influx, since the addition of ATP to the SR suspension can enhance Ca^{2+} uptake as well as Ca^{2+} release.

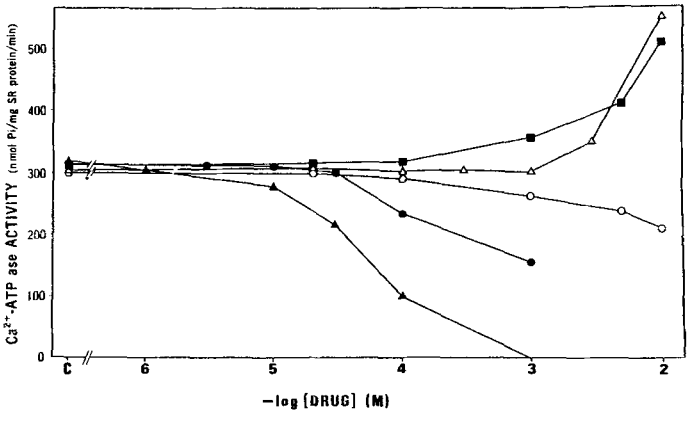

Fig. 5. Effects of the anesthetic and related agents on Ca^{2+}-ATPase activity. ATPase activity was defined at 27°C as the difference between the ATPase activities measured in the presence of 10μ free Ca^{2+} and 1 mM EGTA with no addition of Ca^{2+}. Experimental conditions: 20 mM MOPS (pH 7.0) containing 0.1 M KCl, 5 mM $MgCl_2$, 1 mM ATP and 100 μg protein/ml. C indicates the value before the addition of test drugs.

Table 1.

	1 μM	10 μM	0.5 mM	1 mM	5 mM
Ketamine	—	138.1	140.4	—	147.0
Procaine	—	137.9	137.4	—	135.0
Lidocaine	—	138.5	139.3	—	152.7
Succinylcholine	—	138.1	134.0	128.5	—
Pancuronium	138.4	138.1	—	119.5	—

Effects of the anesthetic and related agents on the Ca^{2+} uptake activity. Conditions are the same as in figure 2B. Initial rate of Ca^{2+} uptake was 138 μM Ca^{2+}/min when any drug was not present.

succinylcholine, pancuronium and procaine inhibited the enzyme activity, while ketamine and lidocaine enhanced it in a concentration-dependent manner. Similar tendency was seen with Ca^{2+} uptake activity when the CICR was blocked (fig. 2B, table 1). 100 μM of d-tubocurarine and vecuronium inhibited the Ca^{2+}-ATPase activity by 60% and 50%, respectively, while fentanyl had no effect on the enzyme activity even at 100 μM concentration.

3) Effects of anesthetic and related agents on the maximum storable Ca^{2+} content

As summarized in table 2, ketamine reduced the maximal level of storable Ca^{2+} content at high concentration, while other agents were without significant effects.

Table 2.

		Maximum storable calcium content
Control		300
Ketamine	0.3 mM	300
	10 mM	240
Procaine	5 mM	380
	10 mM	400
Lidocaine	5 mM	320
	10 mM	340
Succinylcholine	1 mM	300
Pancuronium	0.5 mM	300
	1 mM	320

Effects of the anesthetic and related agents on the maximum storable Ca^{2+} content of SR (μM Ca^{2+}/mg SR protein). Conditions are the same as in figure 3.

Discussion

Many lines of evidence have accumulated to indicate that Ca^{2+} regulation by the SR is genetically defective in MH skeletal muscles[2,3]. Some suggestions of abnormality in the Ca^{2+} transport, particularly in CICR of SR[25-27], have led us to examine the effects of anesthetic and related agents on the CICR from SR. The heavy fraction of SR is known to be more useful for studying the CICR mechanism than the light fraction[18,28-31]. In the presence of ATP, however, it is difficult to demonstrate the CICR from the heavy fraction of SR, which requires Ca^{2+} preloading unless caffeine or some potentiator is present (fig. 3)[9,18,32]. The present study showed the Ca^{2+} release induced by caffeine when SR was preloaded with physiological Ca^{2+} concentration (fig. 2A). The effects on the unidirectional rate of Ca^{2+} uptake were also measured (fig. 2B, 5). The effects of the drugs on the CICR were estimated by the net Ca^{2+} release and the unidirectional Ca^{2+} uptake. MH muscles are thought to be more sensitive to caffeine-induced contracture test than normal muscle, in either human or animal[13]. Therefore, our study using the anesthetic concentrations ranging from clinical dosage to much higher level is useful for predicting anesthetic triggering of MH.

The inhibitor of Ca^{2+}-ATPase enhances the net Ca^{2+} release unless CICR were depressed. As shown in figure 6, pancuronium suppressed the net Ca^{2+} release despite inhibitory effect on Ca^{2+}-ATPase, indicating that the drug inhibits the CICR. Similar inhibitory effects on CICR are suggested by succinylcholine and procaine, though succinylcholine caused only small inhibition of the net Ca^{2+} release at high concentration. The inhibition of CICR can also be explained by the fact that no reduction of the maximum storable Ca^{2+} content was obtained with pancuronium, succinylcholine and procaine (table 2). Since succinylcholine dissolved in water is in a charged form, it is uncertain that succinylcholine at clinically relevant concentrations can enter the myoplasm and exerts any significant effect on SR. The drug probably trigger MH via the fasciculations which can release Ca^{2+} into the myoplasma in turn leading to the CICR[33].

The activator of Ca^{2+}-ATPase depresses the net Ca^{2+} release if CICR were not potentiated. Caffeine increases the sensitivity of CICR mechanism to Ca^{2+} and ATP. This potentiating action of caffeine on CICR is supported by the fact that the drug activates Ca^{2+}-ATPase and enhances the net Ca^{2+} release from fragmented SR[18]. No significant increase of the net Ca^{2+} release was obtained with ketamine or lidocaine. Effect of neither ketamine nor lidocaine on the CICR can be inferred only from these observations, since the net Ca^{2+} release is determined by the balance between Ca^{2+} efflux and Ca^{2+} influx. The activator of Ca^{2+}-ATPase also increases the maximum amount of storable Ca^{2+} content in SR, if CICR were not enhanced. Ketamine, unlike lidocaine, decreased the maximum Ca^{2+} content (table 2). It is thus suggested that CICR can be facilitated by high ketamine concentration and that the suppression of net Ca^{2+} release by the drug is due to the enhancement of Ca^{2+} influx mediated by Ca^{2+}-ATPase. Conversely, it is unlikely that lidocaine is a potent facilitator of CICR at any concentration. Ketamine and lidocaine have been incriminated as causative agents

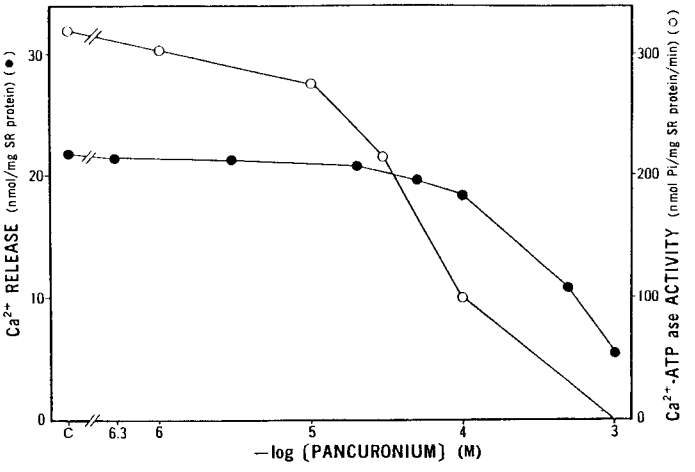

Fig. 6. Effect of pancuronium on the caffeine-induced Ca^{2+} release and the Ca^{2+}-ATPase activity. Conditions and data are the same as in figure 4 and 5. The ordinate indicates the net Ca^{2+} release.

for MH[1,34–36], but some investigators are more skeptical[4,37–42]. Further studies using Ca^{2+} channel isolated should be performed to provide a guide to their potential as triggering agents in MH[43]

The results obtained in the present study lead us to conclude that procaine, lidocaine, non-depolarizing muscle relaxants and opiate are safe for anesthetic maintenance of MHs patients when given in clinical dosage, but ketamine and succinylcholine are not recommended.

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References

1. Cain PA, Ellis FR: Anaesthesia for patients susceptible to malignant hyperpyrexia. A study of pancuronium and methylprednisolone. Br J Anaesth 49:941–944, 1977
2. Gronert GA: Malignant hyperthermia. Anesthesiology 53:395–423, 1980
3. Gronert GA: Malignant hyperthermia, Anesthesia. Vol 2. Edited by Miller RD. New York, Churchill Livingstone, 1986, pp. 1971–1994
4. Paasuke RT, Brownell AKW: Amide local anaesthetics and malignant hyperthermia. Can Anaesth Soc J 33:126–129,1986
5. Endo M, Yagi S, Ishizuka T, Horiuchi K, Koga Y, Amaha K: Changes in the Ca-induced Ca release mechanism in the sarcoplasmic reticulum of the muscle from a patient with malignant hyperthermia. Biomed Res 4:83–92, 1983
6. Ohnishi ST, Taylor S, Gronert GA: Calcium-induced Ca^{2+} release from sarcoplasmic reticulum of pigs susceptible to malignant hyperthermia. The effects of halothane and dantrolene. FEBS Lett 161:103–107, 1983
7. Ohta T, Endo M: Inhibition of calcium-induced calcium release by dantrolene at mammalian body temperature. Proc Japan Acad 62:329–332, 1986
8. Takagi A, Sugita H, Toyokura T, Endo M: Malignant hyperpyrexia. Effect of halothane on single skinned muscle fibers. Proc Japan Acad 52:603–606, 1976
9. Ohnishi ST: Calcium-induced calcium release from fragmented sarcoplasmic reticulum. J Biochem 86:1147–1150, 1979
10. Ogawa Y, Kurebayashi N: The Ca-releasing action of halothane on fragmented sarcoplasmic reticulum. J Biochem 92:899–905, 1982
11. Beeler T, Gable K: Effect of halothane on Ca^{2+}-induced Ca^{2+} release from sarcoplasmic reticulum vesicles isolated from rat skeletal muscle. Biochim Biophys Acta 821:142–152, 1985
12. Kitazawa T, Endo M: Increase in passive calcium influx into the sarcoplasmic reticulum by "Depolarization" and caffeine. Proc Japan Acad 52:599–602, 1976
13. Kalow W, Britt BA, Richter A: The caffeine test of isolated human muscle in relation to malignant hyperthermia. Can Anaesth Soc J 24:678–694, 1977
14. Reed SB, Strobel GE: An in-vitro model of malignant hyperthermia. Differential effects of inhalation anesthetics on caffeine-induced

muscle contractures. Anesthesiology 48:254–259, 1978
15. Rosenberg H: International workshop on malignant hyperpyrexia. Anesthesiology 54:530–531, 1981
16. Gronert GA: Controversies in malignant hyperthermia. Anesthesiology 59:273–274, 1983
17. Nelson TE, Flewellen EH, Gloyna DF: Spectrum of susceptibility to malignant hyperthermia–Diagnostic dilemma. Anesth Analg 62:545–552, 1983
18. Kirino Y, Shimizu H: Ca-induced Ca release from fragmented sarcoplasmic reticulum: A comparison with skinned muscle fibers studies. J Biochem 92:1287–1296, 1982
19. Scarpa A: Measurement of cation transport with metallochromic indicators. Methods in Enzymology 56:301–338, 1979
20. Endo M: Calcium release from the sarcoplasmic reticulum. Physiol Rev 57:71–108, 1977
21. Martin JB, Doty DM: Determination of inorganic phosphate. Modification of isobutyl alcohol procedure. Anal Chem 21:965–967, 1949
22. Ohnishi ST, Flick JL, Rubin E: Ethanol increases calcium permeability of heavy sarcoplasmic reticulum of skeletal muscle. Arch Biochem Biophys 233:588–594, 1984
23. Lowry OH, Rosebrough NJ, Farr AL, Randall RJ: Protein measurement with the folin phenol reagent. J Biol Chem 193:265–275, 1951
24. Harafuji H, Ogawa Y: Re-examination of the apparent binding constant of ethylene glycol bis (β-aminoethyl ether) -N,N,N',N'-tetraacetic acid with calcium around neutral pH. J Biochem 87:1305–1312, 1980
25. Nelson TE: Abnormality in calcium release from skeletal sarcoplasmic reticulum of pigs susceptible to malignant hyperthermia. J Clin Invest 72:862–870, 1983
26. Kim DH, Streter FA, Ohnishi ST, Ryan JF, Roberts J, Allen PD, Meszaros LG, Antoniu B, Ikemoto N: Kinetic studies of Ca^{2+} release from sarcoplasmic reticulum of normal and malignant hyperthermia susceptible pig muscles. Biochim Biophys Acta 775:320–327, 1984
27. Ohnishi ST, Waring AJ, Fang SG, Horiuchi K, Flick JL, Sadanaga KK: Abnormal membrane properties of the sarcoplasmic reticulum of pigs susceptible to malignant hyperthermia: Modes of action of halothane, caffeine, dantrolene, and two other drugs. Arch Biochem Biophys 247:294–301, 1986
28. Miyamoto H, Racker E: Mechanism of calcium release from skeletal sarcoplasmic reticulum. J Membr Biol 66:193–201, 1982
29. Morii H, Tonomura Y: The gating behavior of a channel for Ca^{2+}-induced Ca^{2+} release in fragmented sarcoplasmic reticulum. J Biochem 93:1271–1285, 1983
30. Nagasaki K, Kasai M: Fast release of calcium from sarcoplasmic reticulum vescicles monitored by chlortetracycline fluorescence. J Biochem 94:1101–1109, 1983
31. Kirino Y, Osakabe M, Shimizu H: Ca^{2+}-induced Ca^{2+} release from fragmented sarcoplasmic reticulum: Ca^{2+}-dependent passive Ca^{2+} efflux. J Biochem 94:1111–1118, 1983
32. Kim DH, Ohnishi ST, Ikemoto N: Kinetic studies of calcium release from sarcoplasmic reticulum in vitro. J Biol Chem 258:9662–9668, 1983
33. Galloway GJ, Denborough MA: Suxamethonium chloride and malignant hyperthermia. Br J Anaesth 58:447–450, 1986
34. Mogensen JV, Misfeldt BB, Hanel HK: Preoperative excitement and malignant hyperthermia. Lancet 1:461, 1974
35. Roervik S, Stover J: Ketamine-induced acidosis, fever, and creatine-kinase rise. Lancet 2:1384–1385, 1974
36. Lees DE, Macnamara T: Ketamine-induced hyperthermia–Postictal or malignant? Anesthesiology 47:390–391, 1977
37. Zsigmond EK: Comment; Case History No. 65, Malignant hyperthermia with subsequent uneventful general anesthesia. Anesth Analg 50:1111–1112, 1971
38. Wadhwa RK, Tantisira B: Parotidectomy in a patient with a family history of hyperthermia. Anesthesiology 40:191–194, 1974
39. Adragna MG: Medical protocol by habit–The avoidance of amide local anesthetics in malignant hyperthermia susceptible patients. Anesthesiology 62:99–100, 1985
40. Moore DC: Ester or amide local anesthetics in malignant hyperthermia–Who knows?. Anesthesiology 64:294–296, 1986
41. Wingard DW, Bobko S: Failure of lidocaine to trigger porcine malignant hyperthermia. Anesth Analg 58:99–103, 1979
42. Harrison GG, Morrell DF: Response of MHS swine to I.V. infusion of lignocaine

and bupivacaine. Br J Anaesth 52:385–387, 1980

43. Suarez-Isla BA, Orozco C, Heller PF: Single calcium channels in native sarcoplasmic reticulum membranes from skeletal muscle. Proc Natl Acad Sci USA 83:7741–7745, 1986