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Halothane Induces Calcium Release from Human Skinned Masseter Muscle Fibers

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Background: **An increase in masseter muscle tone in response to halothane or succinylcholine anesthesia (or both) can be observed in healthy persons. Thus the authors compared the fiber-type halothane and succinylcholine sensitivities in human masseter and vastus lateralis muscles.**

Methods: **Masseter and vastus lateralis muscle segments were obtained from 13 and 9 healthy persons, respectively. After chemical skinning of a single fiber and loading the sarcoplasmic reticulum with Ca^{++} 0.16 μM solution, halothane (0.5–4 vol% bubbled in the incubating solution), succinylcholine (0.1 μM to 10 mM), or both sensitivities were defined as the concentration inducing more than 10% of the maximum tension obtained by application of 16 μM Ca^{++} solution. The myofilament response to Ca^{++} was studied with and without halothane by observing the isometric tension of skinned masseter fibers challenged with increasing concentrations of Ca^{++}. Muscle fiber type was determined by the difference in strontium-induced tension measurements.**

Results: **A significant difference in halothane sensitivity was found between type 1 masseter fibers (0.6 ± 0.2 vol%; mean ± SD) *versus* type 1 (2.7 ± 0.6 vol%) and type 2 vastus lateralis muscle (2.5 ± 0.4 vol%). Succinylcholine did not induce Ca^{++} release by the sarcoplasmic reticulum. In the masseter muscle, 0.75 vol% halothane decreased the maximal activated tension by 40% but did not change the Ca^{++} concentration that yields 50% of the maximal tension.**

Conclusions: **The very low halothane threshold for Ca^{++} release from the masseter muscle usually could be counteracted by a direct negative inotropic effect on contractile proteins. However, halothane may increase the sensitivity of the sarcoplasmic reticulum Ca^{++} release to succinylcholine-induced depolarization, leading to an increase in masseter muscle tone. (Keys words: Masseter muscle rigidity; skinned fibers; volatile anesthetics.)**

MASSETER muscle rigidity (MMR) is an exaggerated increase in masseter muscle tone in response to halothane, succinylcholine, or both. Although MMR may herald anesthetic-induced malignant hyperthermia crisis,[1,2] it is also a nonspecific sign and can be seen in healthy persons with exposure to halothane followed by succinylcholine administration.[3,4]

The mechanism by which halothane–succinylcholine anesthesia induces an increase in masseter tone is unknown. Succinylcholine-triggered MMR may be a consequence of membrane depolarization, which activates Ca^{++} release from the sarcoplasmic reticulum (SR). Previously we found a heightened caffeine sensitivity of healthy human masseter muscle fibers.[5] Thus, one possible explanation for the response to halogenated agents also could be an inherent hyperreactivity of the SR to calcium-releasing drugs.[6–9] However, halogenated agents also exert a direct depressive effect on the contractile proteins of type 1 skeletal muscle fibers (slow twitch, fatigue resistant).[10] Halogenated agents thus could simultaneously induce Ca^{++} release from the SR and exert a direct negative inotropic effect. If the net effect on the SR exceeds that on the contractile proteins, the increased myoplasmic Ca^{++} concentration may increase the muscle tone.

The purposes of the current study were (1) to determine the fiber type–specific halothane sensitivities of chemically skinned human masseter muscle fibers and to compare them with those of the vastus lateralis fibers, which are commonly used for *in vitro* contracture testing; (2) to evaluate the effect of halothane on the Ca^{++} sensitivity and maximal Ca^{++} activated force of the contractile proteins of skinned masseter muscle fibers; and (3) to evaluate the effects of succinylcholine on Ca^{++} regulation by the SR.

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Materials and Methods

Skinned Fiber Preparation

With informed consent and institutional approval from the Lille Ethics Committee, small fragments of masseter muscle were obtained from 13 healthy persons (6 female, 7 male; mean age, 25 ± 9 yr) who were undergoing orthognathic or superficial lobe parotid surgery (no masseter muscle involvement). These persons were otherwise healthy, with normal dental occlusion, without trismus or obvious masseter muscle wasting. Vastus lateralis muscle fragments were obtained from nine healthy patients (4 female, 5 male; mean age, 26 ± 6 yr) undergoing routine elective orthopedic surgery of the lower limbs. These persons had normal quadriceps development and were not bedridden. Systematic routine histologic and histochemical analyses performed on the muscle segments did not show obvious myopathic modifications, and the fiber type composition was consistent with those reported in the literature for these muscle groups.[5,11–16]

Chemically skinned single fibers were prepared as previously described by Wood *et al.*[17] Chemical skinning, using a solution containing a high concentration of EGTA (Sigma Chemical Co., St Louis, MO), renders the muscle fiber sarcolemma freely permeable to external solutes.[18] Small muscle fragments were attached at their extremities to maintain their excised length and immediately placed in a skinning solution at 4°C for 24 h. They were transferred to a preserving solution that was identical to the skinning solution except for the addition of 50% glycerol (Merck, Darmstadt, Germany) and stored at −20°C until use (for 1 or 2 weeks). This technique is identical to that used by some other laboratories.[19,20]

Single fibers were dissected from the main fascicle and mounted horizontally between two clamps in a muscle bath, as previously described.[5,10] Resting tension was applied by stretching the fiber by 20% of its initial length. The sarcomere length in our procedure was verified using a calibrated micrometer and corresponded to 2.69 ± 0.14 μm. This technique has been validated using the diffraction of a He-Ne laser beam to correspond to a sarcomere length of 2.7 μm.[21,22] For all experiments described here, the length of the fibers was kept constant to avoid sarcomere length-dependent changes in Ca^{++} sensitivity. All experiments were performed at room temperature (20 ± 1°C).

Solutions and Vapor Anesthetics

The calculation and composition of the solutions used have been published previously.[5,23] Halothane and preservative-free succinylcholine were from Zeneca Pharma (Cergy, France) and Sigma Chemical, respectively. All chemicals were reagent grade. To assess the effects of halothane, the test solutions were equilibrated by continuous bubbling for 20 min with the anesthetic agent. Halothane was mixed with 100% nitrogen using a calibrated vaporizer (Fluotec Mark III; Cyprane, Keighley, UK). The anesthetic concentrations in the gas phase were monitored using an infrared calibrated analyzer (Capnomac; Datex, Helsinki, Finland). The anesthetic concentrations used were 0.5, 1, 2, 3, and 4 vol% halothane. The anesthetic concentrations obtained in the experimental chamber were measured by gas–liquid chromatography (head space technique), as previously described.[10] Based on the anesthetic concentration displaced into the gas phase, the concentrations calculated to be in the experimental solution after 20 min of continuous bubbling were as follows: 0.28 ± 0.02 mM, 0.55 ± 0.05 mM, 1.10 ± 0.08 mM, 1.65 ± 0.11 mM, and 2.20 ± 0.12 mM for 0.5, 1, 2, 3, and 4 vol% halothane (concentrations in the gas phase given by the calibrated analyzer), respectively.

Halothane Sensitivity

The threshold concentration (halothane sensitivity) was defined as the concentration of halothane that first induced a tension greater than 10% of the maximal tension obtained with Ca^{++} 16 μM (pCa 4.8) solution on the same fiber. The SR of the fiber was loaded with Ca^{++} 0.16 μM (pCa 6.8) solution, which itself does not induce a contracture. After 30 s of Ca^{++} loading, fibers were rinsed twice with wash solutions to remove excess Ca^{++} and challenged with a test solution equilibrated with a known halothane concentration for 30 s. If no increase in tension was observed at a given halothane concentration, the fiber was exposed to 40 mM caffeine solution (Prolabo, Fonteney S/Bois, France) to release calcium completely from the SR. Between each successive concentration of halothane, fibers were returned to baseline condition by rinsing with the following sequence: relaxing solution, 40 mM caffeine, and relaxing solution to load with Ca^{++} 0.16 μM solution in the same manner (fig. 1).

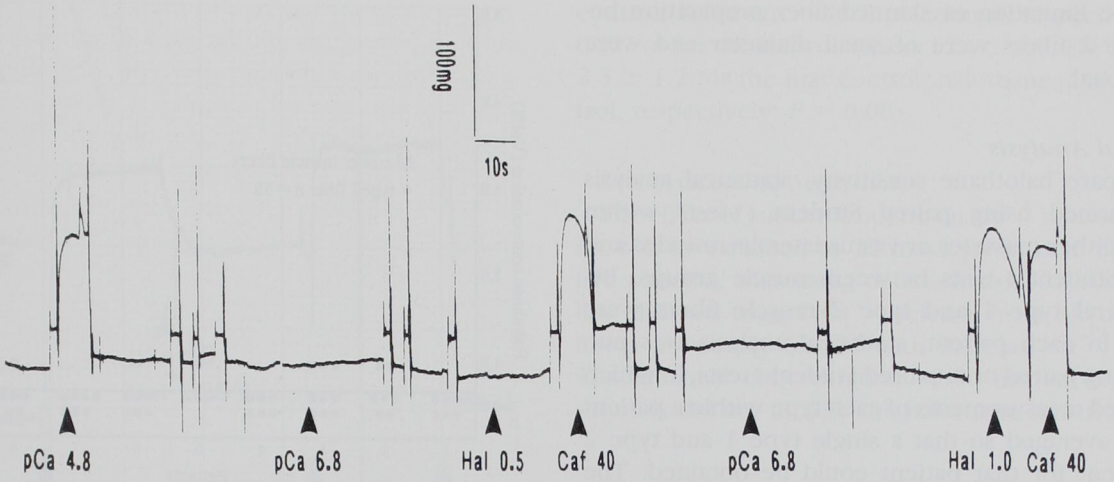

Fig. 1. The sequence for determining halothane sensitivity in human skinned masseter muscle fibers. After the sarcoplasmic reticulum is loaded with Ca^{++} solution (pCa 6.8; pCa = $-\log Ca^{++}$ concentration), the fiber is exposed to a stepwise increase in halothane concentration. No contracture is obtained with 0.5 vol% halothane, but significant contracture (>10% increase in tension) is obtained with 1 vol% halothane (threshold contracture). Hal 0.5, 1, and Caf 40 are 0.5, 1 vol% halothane and 40 mM caffeine solutions, respectively.

Effect of Halothane on the Calcium Sensitivity and Maximal Force of the Contractile Proteins of Masseter Muscle Fibers

For this purpose, the fibers were prepared as described before and then were bathed for 20 min in a relaxing solution containing the nonionic detergent Brij 58 (2%) (Sigma Chemical), which irreversibly eliminates the capacity of the SR to sequester Ca^{++} and to release it under appropriate stimulation but does not affect the contractile proteins.[10] A pCa-tension curve was obtained under control conditions by stepwise exposure of the preparation to solutions with increasing Ca^{++} concentrations and measurements of developed tension. Ca^{++} concentrations ranged from pCa 6.8 ($[Ca^{++}] = 0.16$ μM) to pCa 4.8 ($[Ca^{++}] = 16$ μM), where pCa = $-\log_{10}[Ca^{++}]$. Intermediate tensions were expressed as a percentage of the maximal tension. Data were fit using a nonlinear regression analysis (Enzfitter; Elsevier Biosoft, Cambridge, UK). The same fiber was exposed to a stepwise increase in the Ca^{++} concentration equilibrated with 0.75 vol% halothane. A final pCa-tension curve was obtained with calcium solutions free of anesthetic.

In a second series of experiments, changes of tension at maximal Ca^{++}-activated force were examined using a pCa 4.8 solution in the presence of 0.75 vol% halothane. Each test was preceded immediately and followed by determination of maximal Ca^{++}-activated tension with the control solution (*i.e.*, free of anesthetic).[10] Results were expressed as a percentage of these corresponding control values.

Succinylcholine Sensitivity

The following experimental protocols were performed in EGTA-skinned fibers.[17–20] Pure succinylcholine was diluted with wash solution at the following concentrations: 0.1 μM, 1 μM, 10 μM, 100 μM, and 10 mM. The SR of the fibers was loaded with Ca^{++} 0.16 μM solution for 30 s. Fibers were rinsed twice with wash solutions to remove excess Ca^{++} and challenged with increasing concentrations of succinylcholine. If no increase in tension was observed after exposure to increasing concentrations of succinylcholine, the fiber was exposed to 40 mM caffeine solution to completely release calcium from the SR. In a second set of experiments, the effect of succinylcholine on halothane sensitivity was evaluated. After the halothane sensitivity was determined and the fibers returned to baseline values, the fibers were loaded with Ca^{++} 0.16 μM solution for 30 s and rinsed twice with wash solutions to remove excess Ca^{++}. The fibers were exposed to the maximal concentration of 10 mM succinylcholine for 30 s, and the halothane threshold was determined again. Finally, the fibers were exposed to 40 mM caffeine solution to release calcium completely from the SR.

Muscle Fiber Typing

Fibers were typed by exposure to increasing concentrations of strontium (Sr^{++}; Sigma Chemical), as previously described by Takagi *et al.*[19] and validated in our laboratory.[5] In the current study and in our previous report,[5] the investigation of type 2 masseter muscle was

beyond the limitation of skinned fiber preparation because type 2 fibers were of small diameter and were nonfunctional.

Statistical Analysis

To compare halothane sensitivity, statistical analysis was performed using paired Student *t* tests within groups of either masseter or vastus lateralis muscles and unpaired Student *t* tests between muscle groups. Because several type 1 and type 2 muscle fibers were measured in each patient, statistical analysis was performed using paired or unpaired Student *t* tests, in which the repeated measurements of each type within a patient were first averaged so that a single type 1 and type 2 measurement for that patient could be obtained. The mean difference and standard deviation (SD) of the halothane concentration threshold between the two fiber types in each group of muscle was obtained. For pCa-tension curves in masseter muscle fibers, comparisons of pCa_{50} (the Ca^{++} concentration yielding half-maximal tension) and the Hill coefficient (a measure of the slope of the pCa-tension relation) between control values and 0.75 vol% halothane were made by repeated-measures analysis of variance. Results were expressed as the mean ± SD. Values of $P < 0.05$ were considered significant.

Results

The characteristics of 208 skinned fibers (102 masseter muscle fibers obtained from 13 healthy persons, and 106 vastus lateralis fibers obtained from nine healthy persons) were as follows: length of 1,400 ± 200 μm (SD) for masseter muscle, 1,600 ± 200 μm for vastus lateralis fibers; diameter of 66 ± 16 μm for masseter muscle, and 80 ± 14 μm for vastus lateralis fibers.

Halothane Sensitivity

A total of 164 skinned fibers (58 masseter muscle fibers, 106 vastus lateralis fibers) were tested with increasing concentrations of halothane. Figure 1 shows a typical trace of the determination of halothane sensitivity for a type 1 masseter muscle fiber. Fifty-eight type 1 (100%) masseter fibers and no type 2 (0%) masseter fibers were studied from nine healthy persons. The mean (±SD) halothane threshold for masseter fibers was 0.6 ± 0.2 vol%. Forty-four type 1 (41%) and 62 type 2 (59%) vastus lateralis fibers were studied from nine healthy persons. There was no significant difference between the mean halothane threshold concentration between type 1 (2.7 ± 0.6 vol%) and type 2 fibers (2.5 ± 0.4 vol%) vastus lateralis fibers. The mean (±SD) halothane sensitivity for a given muscle differed between masseter and vastus lateralis fibers. Type 1 masseter fibers had significantly lower halothane sensitivities than did either type 1 and type 2 vastus lateralis fibers ($P < 0.001$; fig. 2).

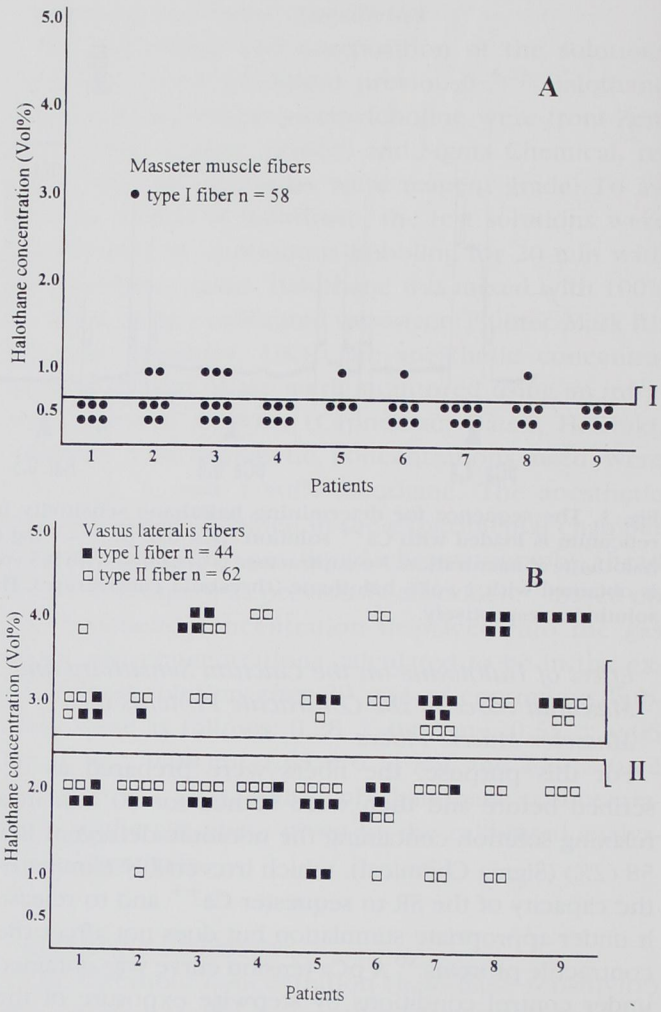

Fig. 2. Halothane sensitivities in human type 1 and 2 skinned masseter and vastus lateralis fibers. The halothane concentration that induced 10% of the maximal contracture with pCa 4.8 solution (pCa = −log Ca^{++} concentration) is shown in panel *A* for each masseter muscle fiber (*circle*) and in panel *B* for each vastus lateralis fiber (*square*). Closed symbol = type 1 fiber; open symbol = type 2 fiber. There was a significant difference in halothane sensitivity ($P < 0.001$) between type 1 masseter muscle fiber (0.6 ± 0.2 vol%) compared with type 1 or type 2 vastus lateralis fibers. There was no significant difference in halothane sensitivity between type 1 (2.7 ± 0.6 vol%) and type 2 (2.5 ± 0.4 vol%) vastus lateralis fibers.

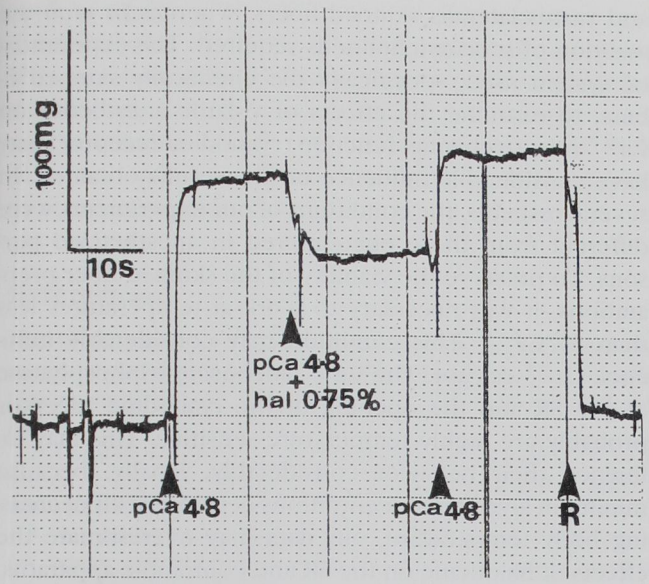

Fig. 3. An example of the changes in maximal activated tension obtained in a skinned masseter muscle fiber during exposure to 0.75 vol% halothane at pCa 4.8 (pCa = −log Ca^{++} concentration). Each exposure to halothane was preceded and followed by determination with the pCa 4.8 control solution alone. Hal 0.75% and R are halothane 0.75 vol% and relaxing solutions, respectively.

Effect of Halothane on Maximal Force and Calcium Sensitivity of the Contractile Proteins of Masseter Muscle Fibers

The effect of halothane on maximal activated tension was determined in 13 masseter muscle fibers obtained from four patients. Maximally activated tension decreased by 40 ± 11% in the presence of 0.75 vol% halothane. Figure 3 shows a typical example. The force traces were obtained when the preparation was activated maximally at pCa 4.8, initially in the absence of halothane. After a substantial increase in force, the fiber was exposed to halothane, which caused a prolonged and stable decrease in force immediately reversible on switching from halothane-equilibrated solution to control solution of identical pCa.

The pCa-tension curves were determined in nine additional masseter muscle fibers obtained from four patients with 0.75 vol% halothane. Tension changes after Ca^{++} changes were plotted and normalized to maximal tension in the same conditions, allowing analysis of the sensitivity of the preparations to Ca^{++} in the absence and in the presence of halothane. Normalized pCa-tension curves were not modified by halothane (fig. 4). Thus, no significant changes were observed for pCa_{50} (6.00 ± 0.33, 6.02 ± 0.30, and 6.01 ± 0.33 for the first control, halothane, and final control, respectively; P = 0.91) or for the Hill coefficient (2.1 ± 0.9, 1.9 ± 0.5, and 2.5 ± 1.2 for the first control, halothane, and final control, respectively; P = 0.08).

Succinylcholine Sensitivity

The effect of succinylcholine on Ca^{++} release from the SR was investigated in 22 masseter muscle fibers from five patients. Increasing concentrations of succinylcholine did not trigger Ca^{++} release from SR of skinned fibers previously loaded with 0.16 μM Ca^{++} solution. The maximal concentration of 10 mM succinylcholine solution did not modify the halothane sensitivity.

Discussion

The main finding of our study is that halothane sensitivity was significantly higher in type 1 human masseter fibers compared with vastus lateralis fibers. This increase in halothane sensitivity results from a direct hypersensitivity of the SR. Because human masseter muscle is composed predominantly of large type 1 fibers,[14,16] although a range of distribution exists within fiber types,[11–15] our results may indicate the presence of a

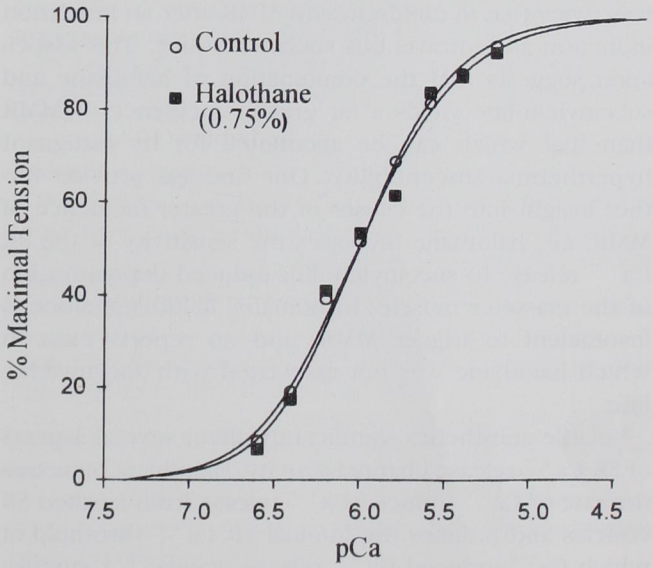

Fig. 4. Mean pCa-relative tension curves (where pCa= −log Ca^{++} concentration) obtained in control conditions and with 0.75 vol% of halothane in nine type 1 masseter skinned fibers. Neither pCa_{50} (the Ca^{++} concentration for half-maximal tension) nor the slope of the tension-pCa relation was significantly different for halothane and control conditions. The control curve represents the mean of the initial and final control conditions.

very low halothane reactivity threshold at this step (SR Ca^{++} release) of the excitation-contraction coupling. This may explain, in part, the ability of the muscle to react to the combination of halothane and succinylcholine[3,24-27] with an increase in muscle tone leading to MMR in extreme cases.[3,4,26-28]

Succinylcholine has no direct effect on SR or contractile proteins. Its action probably is mediated through activation of type 1 masseter fibers that elicited tonic contractions while the drug is present.[29] The resting tension of the masseter muscle increases in a dose-related manner as succinylcholine blocks neuromuscular function.[29] That study was performed in swine, and species differences may prevent this assumption of similar results in humans. Most clinical studies that assessed the effects of succinylcholine administration on jaw stiffness in children were done under halothane[3,24,26,28] or enflurane anesthesia.[4] Our results may explain, in part, why MMR is extremely rare after induction with thiopental followed by succinylcholine (no volatile anesthetic administered).[30] The presence of thiopental is believed to exert a protective effect,[31] and the report by Lazzell *et al.*[32] supports this concept. In a study by Christian *et al.*,[2] the incidence of malignant hyperthermia susceptibility in children in whom MMR developed after an intravenous induction including succinylcholine was twice that in children with MMR after an inhalation induction and intravenous succinylcholine. This association suggests that the combination of halothane and succinylcholine yields a far greater incidence of MMR than that which can be accounted for by malignant hyperthermia susceptibility. Our findings provide further insight into the causes of the greater incidence of MMR; *i.e.,* halothane increases the sensitivity of the SR Ca^{++} release to succinylcholine-induced depolarization of the masseter muscle. In humans, halothane alone is insufficient to trigger MMR, and no reports exist in which halothane was not associated with succinylcholine.

Volatile anesthetics significantly affect several aspects of SR Ca^{++} release channel activity. Halothane increases the rate of Ca^{++}-induced Ca^{++} release from isolated SR vesicles and reduces the luminal SR Ca^{++} threshold at which Ca^{++}-induced Ca^{++} release occurs.[33] A stimulation of the rate constant for SR Ca^{++} release by halothane is also observed with skinned fibers.[6,7] In both SR vesicles and skinned fibers, halothane increases the sensitivity of the SR Ca^{++} release to activating Ca^{++}.[8,9] A perplexing issue regarding the initiation of MMR is that halothane stimulates Ca^{++} release from both masseter and vastus lateralis skinned fibers, whereas *in vivo* the addition of succinylcholine is required. The experimental system used, specifically the chemically skinned fibers, to examine the effects of volatile anesthetics on Ca^{++} release channel function (ryanodine receptor) may have considerable influence on the results obtained. In several respects, the conditions of our experiments were different from those encountered in anesthetized persons. To preserve the viability of the skinned fiber preparations, it was necessary to work at temperatures less than 37°C.[8-10] This condition may considerably influence Ca^{++} release. The Ca^{++} adenosine triphosphatase of the SR and the opening of the ryanodine receptor probably are highly temperature sensitive. This may influence their behavior considerably. Finally, because minimum alveolar concentrations decrease with decreasing body temperature, our data may overestimate the effects of halothane on the SR and contractile apparatus.

Although the effects of volatile anesthetics on calcium sensitivity and the maximal force of contractile proteins have been evaluated extensively, few authors have compared the responsiveness of both type 1 and type 2 skeletal muscles using similar experimental conditions. Our results obtained with type 1 skinned masseter fibers are consistent with those reported by Ohta *et al.*[9] in saponin pretreatment of pig gracilis muscle. In their experiment, the pCa-tension relation of healthy muscle was not altered by halothane.[9] Similarly, Su *et al.*[34,35] found that halothane slightly decreased maximal Ca^{++}-activated tension in soleus muscle (type 1, slow twitch skeletal muscle), whereas halothane produced no change in the adductor magnus (type 2, fast twitch skeletal muscle).

We have no explanation for the difference in the effect of halothane on type 1 masseter compared with type 1 vastus lateralis muscle. A possible role of skeletal muscle–specific myofibril isoforms in the mechanism of halothane depression of contractility has been suggested.[10] Nevertheless, if these results can be extrapolated to *in vivo* conditions, they may partly explain the difference in the overall inotropic action of halothane between masseter and other muscles. Such significant negative inotropic effects on the maximal force of masseter contractile proteins may counteract the low halothane threshold reactivity of the SR. This may explain, in part, the inability of the masseter muscle to react to halothane alone without the presence of succinylcholine.

In conclusion, we found that halothane sensitivity of the SR was significantly greater in the masseter muscle compared with type 1 and type 2 vastus lateralis muscle.

Such a significant effect could be counteracted by a direct negative inotropic effect on contractile apparatus. If these results can be extrapolated to *in vivo* conditions, they may explain why the combination of halothane and succinylcholine yields a far greater incidence of MMR than that which can be accounted for by malignant hyperthermia susceptibility.

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