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Effect of Isoflurane on Motor-evoked Potentials Induced by Direct Electrical Stimulation of the Exposed Motor Cortex with Single, Double, and Triple Stimuli in Rats

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Background: The clinical application of intraoperative motor-evoked potentials (MEPs) has been hampered by their sensitivity to anesthetics. Recently, to overcome anesthetic-induced depression of myogenic MEPs, multiple stimulus setups with a paired or a train of pulses for stimulation of the motor cortex were reported. However, the effects of anesthetics on MEPs induced by these stimulation techniques are unknown.

Methods: Bipolar electrical stimulation of the left motor cortex was carried out in 15 rats anesthetized with thiopental while the compound muscle action potentials were recorded from the contralateral hind limb. After recording of the MEP in response to the single-shock stimulation of the motor cortex, paired pulses (double pulses) or a train of three pulses (triple pulses) with an interstimulus interval of each pulse at 0.3, 0.5, 1.0, 1.5, and 2.0 ms were applied. After control MEP recording, isoflurane was administered at a concentration of 0.25 minimum alveolar anesthetic concentration (MAC), 0.5 MAC, 0.75 MAC, and 1.0 MAC, and the effects of isoflurane on the MEPs induced by single, double, and triple pulses were evaluated.

Results: In all animals, distinct baseline MEPs were recorded. During the administration of 0.25 MAC and 0.5 MAC isoflurane, MEPs induced by stimulation with a single pulse could be recorded in 87% and 33% of animals, respectively,

and MEP amplitude was significantly reduced in a dose-dependent manner. During the administration of 0.75 MAC isoflurane, MEPs after single-pulse stimulation could not be recorded in any animals. By stimulating with paired or triple pulses, the success rate of MEP recording and MEP amplitude significantly increased compared with those after single pulse before and during the administration of isoflurane. Both the success rate of MEP recording and MEP amplitude after double- and triple-pulse stimulation decreased significantly in a dose-dependent manner during the administration of isoflurane.

Conclusions: Application of double or triple stimulation of the motor cortex increases the success rate of MEP recording and its amplitude during isoflurane anesthesia in rats. However, these responses are suppressed by isoflurane in a dose-dependent manner. (Key words: Anesthetics, gases: isoflurane. Monitoring, spinal cord function: motor-evoked potentials; electrical stimulation. Animals: rat.)

INTRAOPERATIVE monitoring of motor-evoked potentials (MEPs) to electrical or magnetic stimulation of motor cortex provides a method for monitoring the functional integrity of descending motor pathways during operations in which there is a risk for brain or spinal cord injury. However, clinical and experimental use of these techniques with a single pulse for stimulation has shown that the elicited potentials are very sensitive to suppression by anesthetic agents, particularly volatile anesthetic agents.¹⁻⁷ The myogenic responses are suppressed in a dose-dependent manner and are completely abolished even with very low concentrations of volatile anesthetic agents, which makes MEP recording impossible.^{1,2,6,7}

To overcome anesthetic-induced depression, several stimulation techniques for monitoring myogenic MEPs have been attempted.⁸⁻¹¹ Kalkman and associates⁸ showed that application of paired transcranial stimuli with an interstimulus interval of 2 to 3 ms significantly increases amplitudes of intraoperative myogenic MEPs

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during anesthetic-induced depression of the motor system. They suggested that this facilitation of myogenic MEPs by paired stimulation occurred when the excitation threshold was lowered by the first stimulus, thereby facilitating the initiation of neuronal discharge by the second stimulus. After the depolarization of the motoneuron, sodium channels open for 1 to 2 ms. After closing the channels, the resulting excitatory postsynaptic potentials (EPSPs) decreases in the next 10 to 15 ms. A second opening of the same channels within this period will result in an augmentation (temporal summation) of the EPSPs. The more rapid the rate of repetitive depolarization, the greater the postsynaptic potential that develops. Taniguchi and colleagues⁹ stimulated the exposed motor cortex with a short train of high-frequency (300 to 500 Hz) rectangular pulses and recorded the compound muscle action potentials (CMAPs) from the muscles under general anesthesia in patients having neurosurgery. They showed that when compared with the traditional way of eliciting movement of the extremities by applying a train of pulses at lower frequency (50 to 60 Hz), muscle responses were obtained at a lower stimulus intensity.

These techniques using an augmentation (temporal summation) of EPSPs seem to be effective for monitoring myogenic MEPs under general anesthesia. However, the effects of anesthetic agents on temporal summation of EPSPs and myogenic MEPs after stimulation of the motor cortex with paired or a train of pulses are unknown. Therefore, in the present study, we evaluated the effect of isoflurane on myogenic motor-evoked potentials induced by electrical stimulation of the exposed motor cortex with paired or triple pulses in rats.

Materials and Methods

This study was approved by the institutional animal care and use committee. Animals were allowed free access to food and water until they were anesthetized. Fifteen male Wistar rats weighing 250 to 350 g were anesthetized with an intraperitoneal injection (100 mg/kg) of thiopental. Subsequent doses of thiopental (50 mg/kg) were administered intraperitoneally if the animal responded to surgical stimulation. After tissue infiltration with 1% lidocaine, the trachea was intubated *via* a tracheostomy and the lungs were ventilated with 100% oxygen using a small-animal respirator (EVM-50A; Aika, Chiba, Japan) to maintain arterial carbon dioxide

tension (P_{aCO_2}) between 35 and 40 mmHg. The right femoral vein and artery were exposed and cannulated for fluid infusion and arterial blood pressure monitoring, respectively. A rectal thermometer monitored the temperature, which was maintained at approximately 36°C with a heating pad. Readings of blood gases were obtained periodically throughout the experiments and maintained within normal range.

The animals were turned prone and the head was fixed in a stereotactic frame. The scalp was infiltrated with 1% lidocaine and reflected laterally to expose the calvarium. A left parasagittal craniectomy was performed using a drill with the aid of a surgical microscope, and the epidural cortical surface was exposed. Bipolar stimulation of the sensorimotor cortex was performed using two stainless steel ball electrodes (1 mm in diameter) placed on the cortical surface approximately 2 mm posterior to the coronal suture near the midline. The distance between electrodes was 2 to 3 mm. Two standard recording needle electrodes were inserted in the right hindlimb. A grounding electrode was placed over the tail. Constant current stimulation was delivered through an electrical stimulator (SEN-3301, Nihon Koden, Japan). The strength of the electrical stimulus was gradually increased until the CMAP no longer increased in amplitude. No averaging was necessary. Low-cutoff and high-cutoff filters were set at 0.3 and 3,000 Hz, respectively. After recording the CMAP in response to the single-shock stimulation, electrical stimulation with paired pulses or a train of three pulses was performed. The duration of each pulse was 200 μ s. Interstimulus interval of each pulse was changed at 0.3, 0.5, 1, 1.5, and 2 ms.

After control CMAP recording, isoflurane was administered at an inspired concentration equal to 0.25 MAC and then initiated in a stepwise manner to 0.5 MAC, 0.75 MAC, and 1 MAC. After at least 15 min of isoflurane administration at each concentration, CMAPs in response to single-shock stimulation and stimulation with paired pulses (double pulses) or a train of three pulses (triple pulses) were recorded. Isoflurane was administered from concentration-calibrated agent-specific vaporizers (Forawick, Murako, Japan). The inspired concentration of volatile anesthetic agents was monitored using an anesthetic gas analyzer (anesthetic agent monitor; Acoma, Tokyo, Japan). As determined from the literature,¹² MAC for isoflurane was accepted as 1.4 vol%. At the end of each experiment, the animal was killed by an overdose injection of thiopental.

Table 1. Amplitude (μ V) of Myogenic MEPs in Response to Electrical Stimulation of Motor Cortex in 15 Rats

	Control	Isoflurane			
		0.25 MAC	0.5 MAC	0.75 MAC	1.0 MAC
Single pulse	319 \pm 106	117 \pm 47†	3 \pm 2†	0†	0†
Double pulses					
ISI 0.3 msec	366 \pm 137	158 \pm 82*	7 \pm 3†	1 \pm 1†	0†
0.5 msec	471 \pm 145‡	239 \pm 97*§	20 \pm 7†‡	9 \pm 5†	4 \pm 2†
1.0 msec	758 \pm 242§	264 \pm 71†§	40 \pm 7†§	13 \pm 5†§	5 \pm 3†
1.5 msec	624 \pm 143‡	247 \pm 78†§	38 \pm 9†§	11 \pm 4†‡	3 \pm 2†
2.0 msec	484 \pm 85‡	232 \pm 66†§	30 \pm 5†§	13 \pm 5†‡	3 \pm 2†
Triple pulses					
ISI 0.3 msec	460 \pm 144‡	263 \pm 104*§	24 \pm 10†‡	9 \pm 5†	4 \pm 2†
0.5 msec	605 \pm 119§	292 \pm 89†§	42 \pm 9†§	16 \pm 6†§	4 \pm 2†
1.0 msec	864 \pm 260†§	325 \pm 77†§	66 \pm 14†§	23 \pm 6†§	8 \pm 4†‡
1.5 msec	648 \pm 141†‡	282 \pm 74†§	48 \pm 9†§	19 \pm 5†§	6 \pm 2†‡
2.0 msec	703 \pm 248‡	317 \pm 109†§	43 \pm 8†§	14 \pm 5†§	4 \pm 2†

Data are mean \pm SEM.

ISI = interstimulus interval; MAC = minimum alveolar anesthetic concentration.

* $P < 0.05$ versus control.

† $P < 0.01$ versus control, by one-way ANOVA with repeated measurement.

‡ $P < 0.05$ versus single pulse.

§ $P < 0.01$ versus single pulse, by Wilcoxon signed ranks test.

To compare mean arterial pressure and amplitude and latency of myogenic MEPs during the administration of isoflurane, one way analysis of variance with repeated measures was used. Differences in amplitude between single and double stimulation and between single and triple stimulation were compared using Wilcoxon signed ranks test. Results are considered significant at $P < 0.05$. Data are expressed as mean \pm SEM.

Results

In all animals, distinct baseline responses were obtained. The CMAP consisted of a multiphasic wave form in most animals. The amplitude of CMAPs after single stimulation varied between 30 and 1,660 μ V. The onset latencies of CMAP after single stimulation ranged from 3.5 to 5.6 ms. The amplitudes of CMAP after stimulation of double pulses at an interstimulus interval of 0.5, 1, 1.5, and 2 msec were significantly larger than those after single-pulse stimulation. Amplitudes of CMAP after stimulation of triple pulses at an interstimulus interval of 0.3, 0.5, 1, 1.5, and 2 ms were significantly larger than those after single-pulse stimulation. Table 1 summarizes changes in amplitude of CMAPs. The largest CMAP amplitude occurred with a 1-ms interstimulus interval for both double and triple pulses.

Figure 1 shows representative CMAPs during the administration of isoflurane. During the administration of 0.25 MAC and 0.5 MAC isoflurane, CMAPs after single-pulse stimulation could be recorded in 13 animals (87%) and five animals (33%), respectively, and amplitudes of CMAPs were significantly reduced to 29.5% and 0.9%, respectively. During the administration of 0.75 MAC isoflurane, CMAPs after single-pulse stimulation could not be recorded in any animals.

Figure 2 shows the changes in success rate of CMAP recording after single-, double-, and triple-pulse stimulation before and during the administration of isoflurane. Success rates were greater after double- and triple-pulse stimulation than after single-pulse stimulation. Figure 3 shows representative CMAPs after single-, double-, and triple-pulse stimulation during the administration of 0.5 MAC isoflurane.

Table 1 shows changes in CMAP amplitude after single-, double-, and triple-pulse stimulation before and during the administration of isoflurane. Amplitudes after double- and triple-pulse stimulation significantly decreased in a dose-dependent manner during the administration of isoflurane. Figure 4 shows the percentage changes in CMAP amplitude of the control value (amplitude after single-pulse stimulation before the administration of isoflurane) after single-, double-, and triple-pulse

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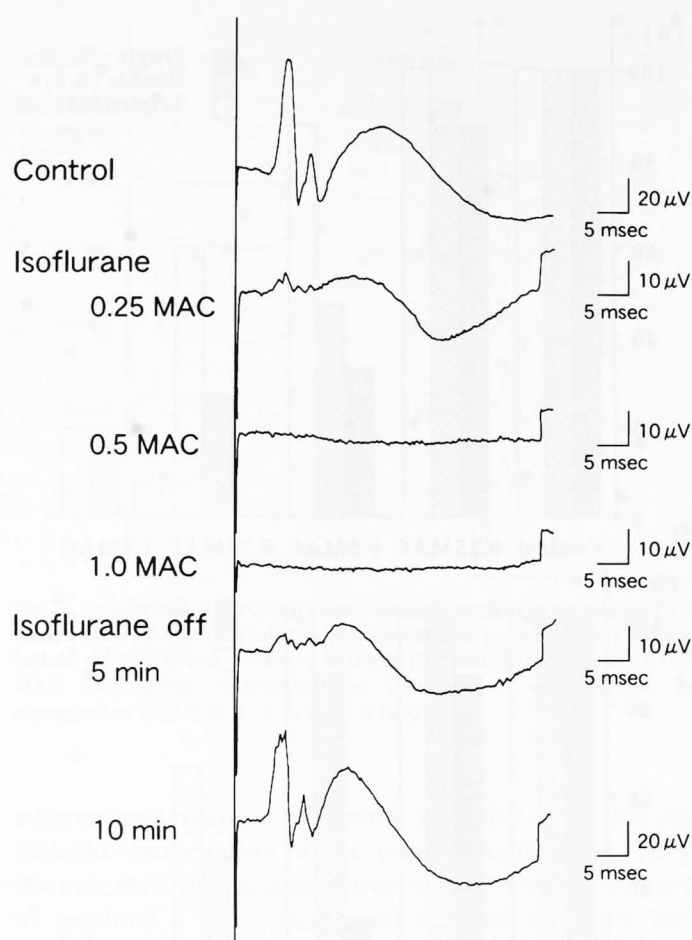


Fig. 1. Representative compound muscle action potentials induced by electrical stimulation of the motor cortex with a single pulse before, during, and after administration of isoflurane in the rat. MAC = minimum alveolar anesthetic concentration.

stimulation before and during the administration of isoflurane.

The latencies of CMAPs after single stimulation were 4.6 ± 0.1 ms ($n = 15$), 4.7 ± 0.2 ms ($n = 13$), 4.5 ± 0.2 ms ($n = 5$), and 4.5 ms ($n = 1$) before and during the administration of 0.25 MAC, 0.5 MAC, and 0.75 MAC isoflurane, respectively. Latencies did not change significantly during the administration of isoflurane.

The values of mean arterial pressure before and during the administration of 0.25 MAC, 0.5 MAC, 0.75 MAC, and 1 MAC isoflurane were 119 ± 3 mmHg, 111 ± 3 mmHg, 108 ± 4 mmHg, 109 ± 3 mmHg, and 105 ± 3 mmHg, respectively. Slight but significant reductions of mean arterial pressure were noted during the administration of isoflurane.

Discussion

The results obtained in the present study reveal that although the success rate of myogenic MEP recording and amplitude of myogenic MEP after double- and triple-pulse stimulation are larger than those after single-pulse stimulation during the administration of isoflurane, both success rates and amplitudes of myogenic MEPs after double- and triple-pulse stimulation decreased dose dependently during the administration of isoflurane.

Haghighi and coworkers⁶ examined the effect of isoflurane on MEPs induced by a single-shock stimulation of the motor cortex in 14 rats. They documented that an increase in isoflurane concentration from 0.3% to 1.5% resulted in a progressive increase in the muscle response latency and a decrease in peak-to-peak amplitude. Zentner and colleagues⁷ studied the effects of halothane, enflurane, and isoflurane on myogenic MEPs induced by direct electrical stimulation of the motor cortex with a single pulse in 10 rabbits; they showed that MEP responses were suppressed in a dose-dependent manner and were absent beyond 0.5 MAC for all inhaled anesthetics tested. These findings are compatible with those obtained in the present study.

Although the precise site at which myogenic MEPs are suppressed by isoflurane is unknown, synaptic transmission has been regarded as the primary site of anesthesia. Zentner and colleagues⁷ suggested that the descending impulse elicited by electrical stimulation of the motor cortex during anesthesia with inhaled anesthetics was inhibited mainly at the level of the spinal interneuronal or motoneuronal systems. When the descending impulses are inhibited, temporal accumulation of several EPSPs is required to bring motor neurons from the resting state to the firing threshold.^{13,14} The EPSPs elicited to motor neurons by a single activation of the corticomotoneuronal tract are reported to last 7 to 10 ms.¹⁵ Taniguchi and colleagues⁹ showed that accumulation of EPSPs at motor neurons could in theory be expected when a short train of rectangular pulses is delivered to the primary motor cortex with an interstimulus interval shorter than 7 ms, that is, at a frequency higher than 150 Hz.

Bannister and Porter¹⁵ reported the results of electrical stimulation of the exposed medullary pyramidal tract in rats anesthetized with pentobarbital. Single stimuli did not produce any movements of the contralateral limbs even when these shocks were intense enough to excite local ipsilateral musculature by direct spread,

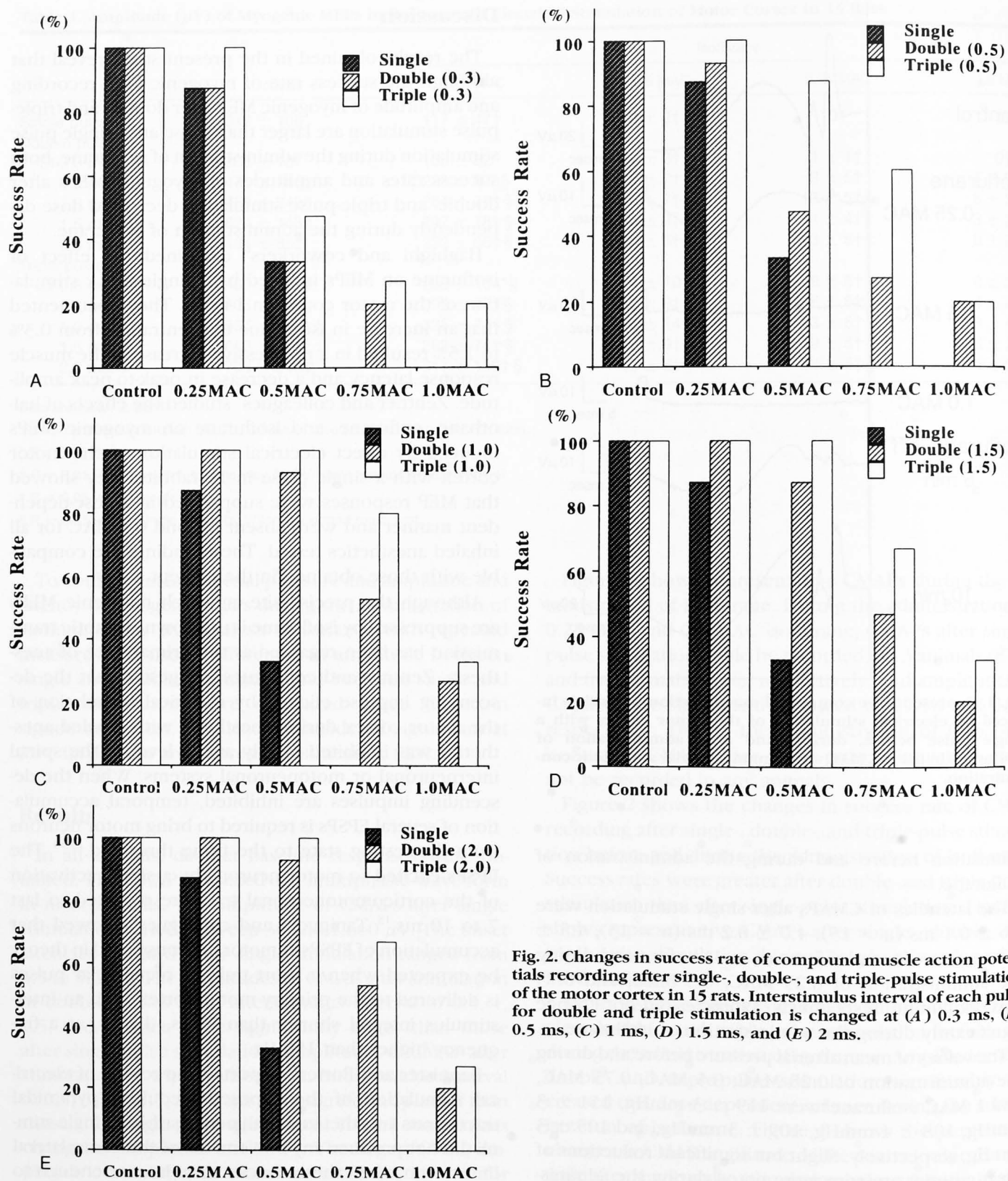


Fig. 2. Changes in success rate of compound muscle action potentials recording after single-, double-, and triple-pulse stimulation of the motor cortex in 15 rats. Interstimulus interval of each pulse for double and triple stimulation is changed at (A) 0.3 ms, (B) 0.5 ms, (C) 1 ms, (D) 1.5 ms, and (E) 2 ms.

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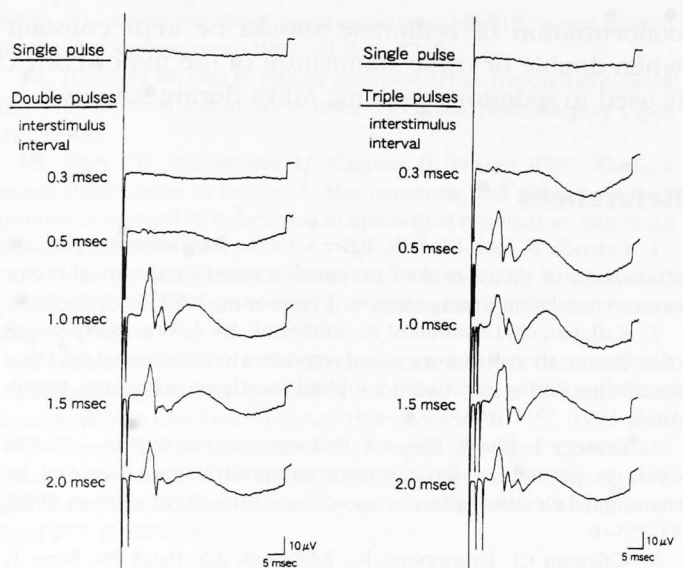


Fig. 3. Representative compound muscle action potentials after single-pulse, double-pulse (*left*), and triple-pulse (*right*) stimulation of the motor cortex during the administration of 0.5 MAC isoflurane. Interstimulus interval of each pulse is changed at 0.3, 0.5, 1, 1.5, and 2 ms.

whereas repetitive stimuli were effective in producing flick-like movements of the contralateral limbs. They documented that at least three shocks were necessary to produce a movement, and that an optimum frequency of stimulation was reached between 300 and 500 Hz. When three stimuli at 500 Hz were delivered to the pyramidal tract, the EPSP recorded at the lumbar motoneurons with intracellular microelectrodes was larger than that produced by single shocks or pairs of shocks at the same intensity. These results are consistent with the results obtained in the present study, in which success rate and amplitude of MEPs after double and triple stimulation were greater than those after single stimulation. However, the effects of anesthetics on myogenic MEPs induced by repetitive stimulation of the motor cortex are unknown. To our best knowledge, this is the first report to evaluate the relationship between the motor response to repetitive stimulation of the motor cortex and increasing concentrations of volatile anesthetic. Although temporal accumulation of EPSPs at motor neurons may be induced by repetitive stimulation of the motor cortex, such that myogenic MEPs can be recorded even during isoflurane anesthesia, an increase in isoflurane concentration resulted in a progressive decrease in the success rate and amplitude of myogenic MEPs.

In this study, mean arterial pressure decreased significantly when isoflurane was administered. However, it is unlikely that the attenuation of myogenic MEP during the administration of isoflurane is due to reduction of mean arterial pressure because only a slight, but significant, reduction of mean arterial pressure to 105 mmHg was noted. Hitchon and associates¹⁶ showed that graded hypotension down to 40 mmHg did not change spinal cord blood flow, and that spinal cord latency and

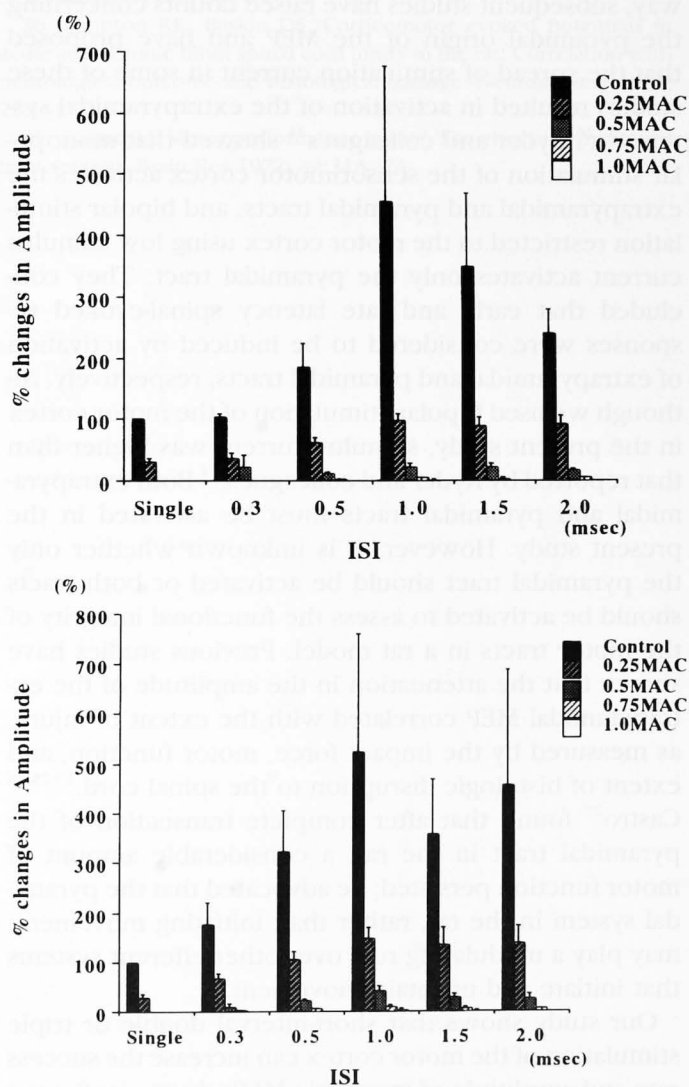


Fig. 4. Percentage changes in compound muscle action potentials amplitude of the control value (amplitude of compound muscle action potentials after single-pulse stimulation before the administration of isoflurane) after single-pulse, double-pulse (a), and triple-pulse (b) stimulation of the motor cortex before and during the administration of isoflurane. Interstimulus interval of each pulse is changed at 0.3, 0.5, 1, 1.5, and 2 ms. Data are expressed as mean \pm SEM.

conduction velocity remained unchanged. Haghighi and Oro¹⁷ studied the effects of hypovolemic hypotensive shock on somatosensory- and motor-evoked potentials in 12 cats and found that latency and amplitude did not change significantly with arterial pressures between 60 and 100 mmHg, and a decrease in amplitude and an increase in latency occurred when arterial pressure decreased to less than 40 mmHg.

Although initial studies suggested that the MEP in the rat arises from activation of the spinal pyramidal pathway, subsequent studies have raised doubts concerning the pyramidal origin of the MEP and have proposed that the spread of stimulation current in some of these studies resulted in activation of the extrapyramidal system.¹⁸⁻²⁴ Ryder and colleagues²⁴ showed that monopolar stimulation of the sensorimotor cortex activates the extrapyramidal and pyramidal tracts, and bipolar stimulation restricted to the motor cortex using low stimulus current activates only the pyramidal tract. They concluded that early and late latency spinal-evoked responses were considered to be induced by activation of extrapyramidal and pyramidal tracts, respectively. Although we used bipolar stimulation of the motor cortex in the present study, stimulus current was higher than that reported by Ryder and colleagues.²⁴ Both extrapyramidal and pyramidal tracts must be activated in the present study. However, it is unknown whether only the pyramidal tract should be activated or both tracts should be activated to assess the functional integrity of the motor tracts in a rat model. Previous studies have shown that the attenuation in the amplitude of the extrapyramidal MEP correlated with the extent of injury, as measured by the impact force, motor function, and extent of histologic disruption to the spinal cord.^{19,25,26} Castro²⁷ found that after complete transection of the pyramidal tract in the rat, a considerable amount of motor function persisted; he advocated that the pyramidal system in the rat, rather than initiating movement, may play a modulating role over other efferent systems that initiate and maintain movement.

Our study shows that short-interval double or triple stimulation of the motor cortex can increase the success rate and amplitude of myogenic MEPs during isoflurane anesthesia compared with single stimulation of the motor cortex. However, because an increase in isoflurane concentration resulted in a progressive decrease of success rate and amplitude of myogenic MEPs induced by not only single stimulation of the motor cortex but also double or triple stimulation of the motor cortex, the

concentration of isoflurane should be kept constant when double or triple stimulation of the motor cortex is used to monitor myogenic MEPs during surgery.

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