We tested the hypothesis that magnetic stimulation of muscle evokes cerebral potentials by causing a muscle contraction that then activates muscle receptors. We measured cerebral evoked potentials accompanying magnetic stimulation of muscle in 3 patients during surgery both before and after muscle paralysis with succinylcholine, a depolarizing agent. The magnetic stimulation was at low intensity (30%) and at a 2/s rate. The administration of succinylcholine sufficient to produce muscle paralysis did not alter cerebral potentials evoked by either low-intensity magnetic stimulation of muscle (gastrocnemius/soleus) or electrical stimulation of peripheral nerve (tibial nerve). In 1 normal subject, the S1 nerve root action potentials conducting at rapid velocity (> 60 m/s) were detected at the S1 foramen with a needle electrode using electrical stimulation of the tibial nerve. However, no S1 nerve root potentials could be identified to magnetic stimulation of muscle that evoked a cerebral potential. We conclude that magnetic stimulation of muscle activates terminal afferents in the muscle to provide the afferent drive for the cerebral potentials independent of muscle contraction. The failure to detect the afferent volley in S1 nerve root to magnetic stimulation suggests that only a few afferents are activated or that the activation of afferents is temporally dispersed.
Key words: somatosensory evoked potentials • magnetic stimulation • muscle afferents • succinylcholine paralysis

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MAGNETIC STIMULATION OF MUSCLE EVOKES CEREBRAL POTENTIALS BY DIRECT ACTIVATION OF NERVE AFFERENTS: A STUDY DURING MUSCLE PARALYSIS

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Magnetic stimulation of the limbs overlying peripheral nerve activates motor nerves at lower threshold than sensory nerves.[9,12,13,20] When the magnet is placed over the muscle belly a contraction is elicited which has been attributed to stimulation of deep motor nerves rather than to direct activation of muscle fibers. A critical experiment was reported by Lotz et al., who noted that the muscle contractions accompanying by magnetic stimulation of muscle were abolished following paralysis with curare.[9] Lotz et al. reasoned that magnetic stimulation of the muscle must activate the deep motor nerve efferents and not the muscle fibers directly to produce muscular contractions. Recently, Machetanz et al. confirmed these results using a local infusion of atracurium to block neuromuscular transmission while magnetically stimulating the paralyzed muscle and recording muscle contraction.[11] All of these results are compatible with the hypothesis that magnetic stimulation of muscle evokes contraction by depolarization of terminal motor nerve branches and not depolarization of muscle fibers.

We have been recording the cerebral potentials accompanying magnetic stimulation of muscle.[18,19] We had considered that the afferent stimulus for evoking these potentials derives from muscle spindle activation accompanying the muscle contraction. The participation of muscle spindle afferents as the afferent source for cerebral evoked potentials had been implicated in the evoked potentials accompany-

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ing stretching of the muscle by rapid mechanical movements at the joint, or by tendon taps.[1,4,15] These latter methods were assumed to provide a relatively pure form of Ia afferent activation to the nervous system.

We wished to directly test the hypothesis that magnetic stimulation of muscle evoked cerebral potentials via the muscle contraction's activation of muscle receptors. We measured cerebral evoked potentials accompanying magnetic stimulation of muscle in 3 patients during surgery both before and after muscle paralysis with succinylcholine, a depolarizing agent. The results did not support the hypothesis and showed instead that the evoked potentials accompanying magnetic stimulation of muscle were still elicited during muscle paralysis.

METHODS

Three patients were studied in the operating room while undergoing surgery using general anesthesia and muscle paralysis. The patients had cancers which were of the lung (case 1, age 50, male; and case 3, age 58, male) and of the esophagus (case 2, age 42, female). The patients gave informed consent for the evoked potential procedures. They were premedicated with (sodium luminal 0.1 g, atropine, 0.5 mg). Fast-acting agents (diazapan 10 mg and sodium pentothal 0.24 g) were administered intravenously to allow intubation. The anesthesia employed was N_2O (45% with O_2) and intravenous morphine (20 mg). Succinylcholine (400 mg with 5% glucose solution) was administered intravenously intermittently to achieve muscle relaxation.

Recording of Cerebral Evoked Potentials. Evoked potential recordings were initiated in the operating theater prior to administering the barbiturate in case 1 and case 3 (baseline recordings) but only after the induction of anesthesia in case 2. The latter patient was therefore studied postoperatively to define "baseline" evoked potentials.

Two types of stimuli were used to evoke cerebral potentials: (1) magnetic stimulation of gastrocnemius muscle; and (2) electrical stimulation of tibial nerve at ankle. The methodology used in this study for cerebral potentials evoked by magnetic stimulation of gastrocnemius was similar to that used in our previous experiments.[18]

A MagPro magnetic stimulator (Dantec, Denmark) was used, which could deliver more than 500 stimulations at the intensify of 30% of maximum output (2.1 Tesla) while maintaining the temperature of the coil between 25° and 30°C. A circular magnetic coil (diameter 12 cm, MC 125, Dantec) was placed over the lower half of the left gastrocnemius/soleus muscle and strapped in place. The intensity of stimulation employed (30% of the output) was just sufficient to produce a contraction of the muscle belly underneath the coil, but did not activate the tibial nerve trunk as evidenced by the absence of movements or action potentials of the foot muscles innervated by tibial nerve. Electrical stimulation of tibial nerve at ankle was performed through surface disk electrodes placed over the nerve. The stimulus intensity was suprathreshold and produced a moderate contraction of the abductor hallucis muscle. The stimulus rate in both types of stimulations was 2 Hz. Cerebral evoked potentials were recorded from surface electrodes at Cz′ referenced to Fpz for cases 1 and 3. For case 2 the potentials were difficult to detect at C3′, Cz′, and C4′ reference to Fpz, whereas recordings between Cz′ and C4′ revealed clear potentials to left leg stimuli. The bandpass of recording was 10–1000 Hz and 256 trials comprised an averaged potential. Duplicate averages were made at each time interval.

The protocol in the operating room was to record evoked potentials to magnetic and electrical stimulation in sequence, noting the presence or absence of muscle contraction. Muscle contractions were absent for 1/2 h after administering succinylcholine, allowing the comparison of the evoked potentials with and without muscle contractions being present. The peak latencies and peak-to-peak amplitudes of the components occurring at P40, N50, and P70 were defined.

Recording of Nerve Root Potentials. One of the authors (YZ) served as a subject to define whether afferent potentials could be recorded from the S1 nerve root at the S1 foramen to electrical stimulation of the tibial nerve at the ankle and to magnetic stimulation of the gastrocnemius/soleus muscles. A monopolar needle electromyographic (EMG) electrode was inserted percutaneously into the region of the S1 foramen while stimulating electrically through the needle to evoke a contraction of the calf muscles. The needle was stationed at the site that was optimal for evoking the contraction at minimal current intensity. Potentials were then recorded between the needle electrode and an overlying skin reference electrode while stimulating the tibial nerve at the ankle and the popliteal fossa, respectively, or magnetically activating the calf muscles. Several averages of 50 trials to each form of stimulation was made. Successful nerve recordings could be identified in YZ. We were unable in another author (AS) to define S1 nerve root potential at the S1 foramen to both forms of stimulation.

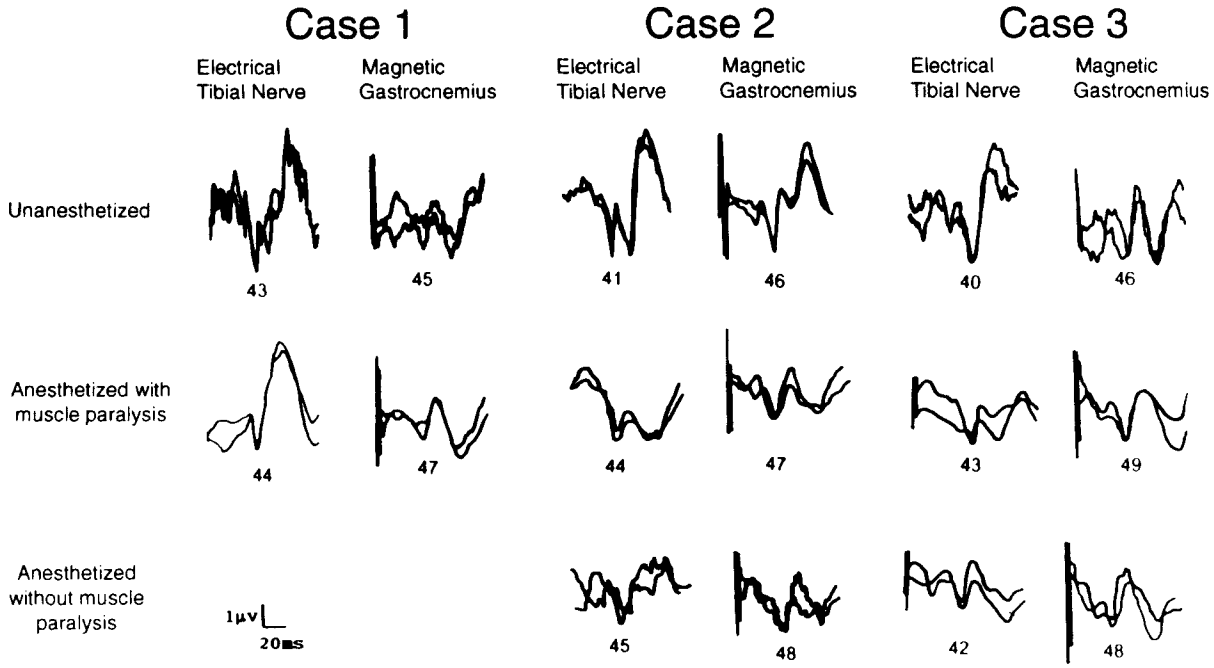

FIGURE 1. Examples from 3 subjects of cerebral potentials accompanying magnetic stimulation of the gastrocnemius/soleus and electrical stimulation of the tibial nerve at the ankle during general anesthesia and muscle paralysis. The peak latency of the first positive cortical component is indicated. Positivity at grid 1 of the amplifier for evoked cerebral potentials is displayed downward in this figure.

RESULTS

Cerebral Evoked Potentials and Succinylcholine. The averaged cerebral evoked potentials from the 3 operative patients are given in Figure 1, and the measures of latency and amplitude of the components are given in Table 1. The cerebral potentials to both electrical stimulation of nerve and to magnetic stimulation of muscle were better defined while the subject was under anesthesia and muscle paralysis than while the subject was unanesthetized and unparalyzed. The difference reflects the effects of paralysis in reducing artifacts from muscle potentials. The anesthetic agents used in these patients increased the latencies of the cerebral potentials to both electrical stimulation of tibial nerve and to magnetic stimulation of calf muscles to a similar degree. However, the cerebral potentials accompanying both electrical and magnetic stimulation were no different in the pres-

Table 1. Comparison of peak latencies and peak-to-peak amplitudes of SEPs to magnetic stimuli to the gastrocnemius in 3 cases during general anesthesia.

	P40			N50			P60		
	Case no.			Case no.			Case no.		
	1	2	3	1	2	3	1	2	3
Peak latency (ms)									
Unanesthetized	45	46	46	55	55	58	72	63	72
Anesthetized with muscle paralysis	47	47	49	58	70	72	75	94	98
Anesthetized without muscle paralysis	—	48	48	—	72	66	—	92	93

	P40–N50			N50–P60		
	Case no.			Case no.		
	1	2	3	1	2	3
Peak-to-peak amplitude (μV)						
Unanesthetized	1.8	2.8	2.8	2.2	1.0	3.0
Anesthetized with muscle paralysis	1.7	1.6	2.5	2.3	1.0	2.2
Anesthetized without muscle paralysis	—	1.8	1.6	—	1.6	1.9

ence or absence of succinylcholine sufficient to produce muscle paralysis (Fig. 1, rows 2 and 3). Thus succinylcholine sufficient to abolish muscle contractions to both electrical stimulation of motor nerve and to magnetic stimulation of muscle had no effect on the accompanying evoked cerebral potentials.

S1 Proximal Nerve Recordings. In one of the authors (YZ) studied while awake and without medications, we were able to record nerve potentials with a needle electrode positioned by the S1 foramen. The potentials were (Fig. 2) approximately 2 μV in amplitude to stimulation of tibial nerve at ankle and at knee. The latencies were 17 ms from the ankle and 7 ms from the knee, providing a conduction velocity over this segment of 54 m/s. The conduction velocity between the knee and the S1 foramen was even more rapid, being 63 m/s. No nerve action potentials could be identified to magnetic stimulation of the calf muscles with stimulus intensities as high as 40%, even though this intensity of stimulation evokes clear cerebral potentials. Above that intensity S1 nerve recordings were contaminated by a stimulus artifact.

DISCUSSION

The present study shows that the administration of succinylcholine sufficient to produce muscle paralysis does not alter cerebral potentials evoked by either low-intensity magnetic stimulation of muscle (gastrocnemius/soleus) or electrical stimulation of peripheral nerve (tibial nerve). Thus, magnetic stimulation of muscle evokes cerebral potentials independent of muscle contraction. There are several mechanisms by which low-intensity magnetic stimulation of the muscles evokes cerebral potentials: (1) direct activation of nerve trunks within the muscle belly; (2) direct activation of muscle spindles or indirect activation of muscle spindles from gamma efferents; and (3) direct activation of terminal muscle afferents.

The evidence to data suggests that magnetic stimulation of nerve trunks first activates the largest and fastest conducting fibers similar to the experience with percutaneous electrical stimulation.[2,7,10] Mag-

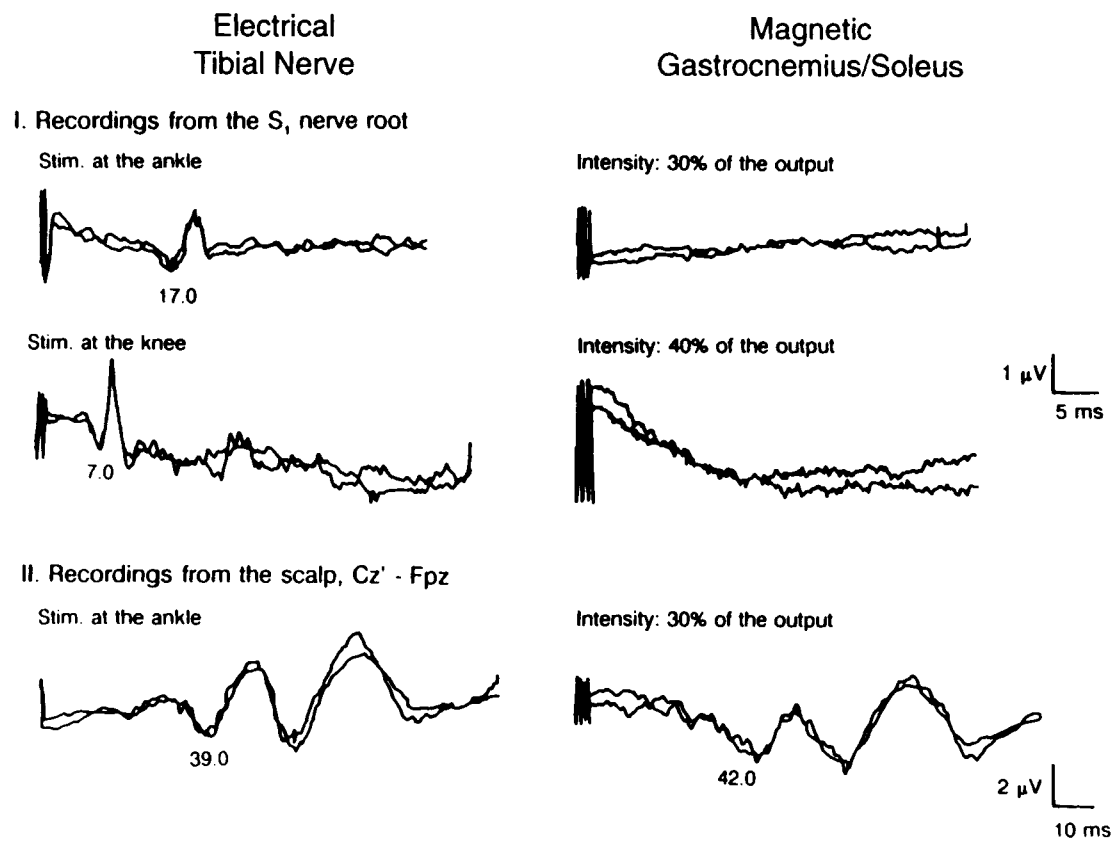

FIGURE 2. Compound nerve action potentials recorded from the S1 nerve root at the S1 foramen of a normal subject after electrical stimulation to the tibial nerve. Note the absence of the nerve root action potentials but the well-developed cerebral evoked potentials after magnetic stimulation to the gastrocnemius/soleus muscle in the left leg. The first cortical positive potential after magnetic stimulation to the gastrocnemius/soleus has a longer latency than to electrical stimulation of the tibial nerve at the ankle.

netic stimulation can activate peripheral nerve trunks to produce somatosensory evoked potentials (SEPs) if stimulus levels are sufficiently high and the nerve trunk is relatively superficial.[2,8,14,16,17] These requirements make it unlikely that the SEPs evoked by stimulation of the gastrocnemius/soleus result from stimulation of the nerve trunk. First, the intensity of stimulation used was of too low an intensity (30% of the maximal output) to activate even a superficially placed nerve trunk.[17] Second, the intensity of magnetic stimulation employed in these studies did not activate the efferent nerve fibers of nerve trunks passing through the calf, as contractions of distal muscles were never observed. Third, the activation of Ia afferents of the nerve trunks passing through the calf requires a much higher-intensity magnetic stimulation (> 80%) than was used to evoke cerebral potentials (30%).[20] Finally, if the magnetic stimulus activated afferents fibers in deep nerve trunks to account for the cerebral potentials, their latency should have been approximately intermediate (i.e., 37 ms) between those accompanying stimulation of the nerve trunk when it becomes superficial at the ankle (circa 40 ms) and at the popliteal fossa (circa 35 ms). The 42-ms latency of the first cerebral component from magnetic stimulation of the calf muscles is not in the proper latency range for the possibility of its origin from magnetic activation of the nerve trunks within the calf.

It is also unlikely that magnetic stimulation of gastrocnemius/soleus activates muscle receptors directly since the latencies of the cerebral components are delayed approximately 10 ms relative to the potentials evoked when muscle spindles in calf muscles are mechanically activated by a tendon tap.[4] The possibility that this delay in latency could be attributable to magnetic stimulation first activating gamma efferents which in turn caused muscle spindle afferent discharge is also untenable since succinylcholine administration, which blocks neuromuscular transmission (and we assume as well for the gamma-intrafusal synapse) did not alter the latency or amplitude of cerebral potentials from magnetic stimulation of calf muscles.

We are left with the third possibility that magnetic stimulation of calf muscles activates terminal nerve afferents in the muscle to provide the afferent drive for the cerebral potentials. This is similar to the manner by which low-intensity magnetic stimulation of muscle induces muscle contraction by activating the terminal nerve efferents and not the muscle fibers directly.[9] The mechanism by which the terminal nerve fibers appear to have a different response capability than the deep nerve trunks may be due to the fact that nerve trunks lie deep to the gastrocnemius/soleus muscles. Finally, results from the present study determined that muscle paralysis does not affect the definition of cerebral potentials to magnetic stimulation of muscle, eliminating the possibility that they are the consequence of muscle contraction induced activation of muscle spindles.

The type of afferent fibers in muscle activated by magnetic stimulation was not revealed by the nerve root recording performed in the present studies. While nerve action potentials conducting at rapid velocity (> 60 m/s) were detected at the S1 foramen using electrical stimulation of the tibial nerve, no nerve potentials could be identified to magnetic stimulation at an intensity sufficient for eliciting both muscle contraction and cerebral evoked potentials. Any conclusion based on 1 subject is a problem. However, if the results were accurate then the failure of magnetic stimulation to evoke a recordable nerve root potentials may be due to: (1) the low numbers of afferent nerve fibers that can be recruited by the induced sinusoidal currents from magnetic stimulation; and/or (2) by temporal dispersion of the action potentials of those fibers activated due to the nonfocused characteristics of the currents accompanying magnetic stimulation.[3] In addition, (3) the needle recording electrode at the sacral foramen has been recording predominantly from S2 nerve root rather than S1 nerve root. Gastrocnemius/soleus muscles are innervated by S1 and S2 nerve roots, but predominantly by S1 nerve root. In spite of these limitations, cerebral potentials of robust amplitude were evoked, reflecting amplification by central somatosensory structures of reduced peripheral input.[5,6] The latency of the cerebral potentials evoked by magnetic stimulation of muscle is considerably longer than what would have been anticipated from direct activation of the terminals of Ia afferents within the calf muscles. The delayed latency may be accounted for by modifications of central sensory transmission. Thus the small number of Ia afferents activated and/or their temporal dispersion is associated with slowed depolarization of central synapses in the somatosensory pathway, resulting in a delay in the latency of the cerebral potentials.

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