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Spinal Cord Microstimulation Generates Functional Limb Movements in Chronically Implanted Cats

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Spinal cord injuries disrupt the communication between the brain and peripheral nerves, but leave motoneurons and networks of interneurons below the level of the lesion intact. It is therefore possible to restore some function following injury by providing an artificial stimulus to the surviving neurons below the level of the lesion. We report here on a novel approach for generating functional movements by electrically stimulating the spinal cord through chronically implanted ultrafine, hair-like electrodes. Six to 12 microwires were implanted in the lumbar enlargement of intact cats for 6 months. Twice a week, trains of stimuli were delivered through each microwire and the evoked electromyographic and torque responses were recorded. Strong coordinated hindlimb movements were obtained by stimulating through individual electrodes. The joint torques elicited were capable of supporting the animals' hindquarters. The responses were stable over time and the contractions caused no apparent discomfort to the animals. No obvious motor deficits were seen throughout the 6-month duration of implantation. The results demonstrate that microwires implanted in the spinal cord remain stably in place and stimulation through these electrodes produces strong, controllable movements. This provides a promising basis for the use of spinal cord neuroprostheses in restoring mobility following spinal cord injury. © 2000 Academic Press

Key Words: **spinal cord injury; electrical stimulation; neuroprostheses; microelectrode stability; control of movement; chronic implants.**

INTRODUCTION

Recovery of function following spinal cord injury remains a daunting medical challenge. The difficulty in achieving regeneration of functional neural connections in the central nervous system has prompted the development of systems that use electrical stimulation of muscles or nerves to improve respiration, micturition, and motor function (16). Intramuscular, epimysial, or nerve cuff electrodes are used to activate muscles. Though some neural prostheses have been successful (e.g., diaphragm pacers (3) and foot-drop stimulators (20)), the electrical restoration of whole limb movements remains problematic (11, 16). Spinal cord microstimulation (SCμstim) may provide an alternative. Ultrafine electrodes placed in the ventral horn can activate limb muscles through ensembles of interneurons and motoneurons. The spinal cord is distant from moving muscles, so electrodes are less likely to be dislodged or damaged. The lumbar enlargement of the cord is relatively short (~5 cm in adult humans), allowing activation of the main limb muscles by electrodes implanted in a small, protected region. Previous experiments in sodium pentobarbital-anesthetized cats showed that muscles can be selectively activated by SCμstim to produce smooth, graded contractions with little fatigue (7–9, 18). However, the question remained whether the same selectivity would pertain in the nonanesthetized spinal cord and whether implanted electrodes would remain stably in place. This is the first full report showing that these prerequisites of a viable spinal neuroprosthesis can be met.

METHODS

Arrays of 6 to 12 microwires were implanted in the lumbosacral region of the spinal cord of healthy, adult cats. The techniques of implantation and electrode stabilization were based on those developed for chronic recordings from single neurons in spinal dorsal roots (10). Placement of the microwires was based on maps established in acute experiments (8, 9). The wires were precut and bent to an appropriate angle and length so once they were inserted in the spinal cord (to a depth of 3.5 to 4.5 mm), their epidural portions lay flat on the dura mater (Fig. 1). Animals were maintained from 2 to 24 weeks (mean 9 weeks) following surgery. Intact animals were used to test the stability of intraspinal microstimulation under the most demanding conditions: free, normal bodily movement. We were partic-

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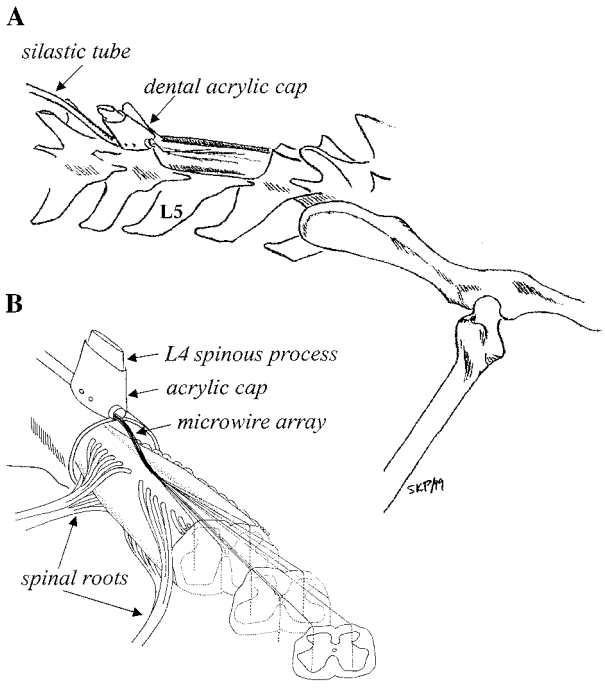

FIG. 1. Microelectrode implantation and fixation in the spinal cord. (A) The dorsal surface of vertebra L5 was removed and the Silastic tube containing the microwires was anchored to the L4 spinous process. (B) The microwires targeted motoneuron pools located in the ventral horn of the spinal cord.

ularly interested in the quality of the movements that could be elicited from within the active, nonanesthetized spinal cord and in determining whether the stimulation caused discomfort.

Surgical procedure. Six healthy adult cats (2–3.5 kg) were used for the experiments. The experimental protocol was approved by the University of Alberta Animal Welfare Committee. Anesthesia was induced with an intraperitoneal injection of sodium pentobarbital (40 mg/kg) and maintained with a 1:5 saline dilution of the anesthetic administered as needed through the cephalic vein. Surgery was conducted under aseptic conditions. The hindlimbs and back were shaved and a skin incision was made from the L4 to L6 vertebral spinous processes. The dorsal surface of vertebra L5 was removed to expose spinal cord segments L5 to S1. Six to 12 microwire electrodes [30-μm stainless-steel wires (California Fine Wire, Gover City, CA), 30- to 70-μm tip exposure, 10- to 30-kΩ impedance] contained within a Silastic tube and attached to a connector on one end were passed subcutaneously from the back incision to the head. The connector was embedded in dental acrylic secured to the skull by screws and the Silastic tube was anchored to the L4 spinous process (10). The microwires emerging from the tube were tethered to the dura mater with 8/0 ophthalmic sutures and further bonded with cyanoacrylate glue. The indifferent electrode [5-cm length of bared stainless-steel wire (Cooner AS632, Chatsworth, CA)] was placed in the back muscles close to the vertebral column. The microwires were inserted through minute holes made in the dura mater with a 30-gauge dental needle on both sides of the spinal cord, 2 mm from the midline. Stimulation through each electrode was used to guide final placement. A small piece of plastic thin film, serving as a barrier to the growth of connective tissue in and around the electrodes, was spot-glued over the dura mater and microwires with cyanoacrylate. The back wound was sutured closed in layers and the cats recovered in an intensive care unit for 1 to 2 days. Animals received 12 hourly doses of a strong opioid analgesic (buprenorphine) during the recovery period. In two cats, pairs of electromyographic (EMG) electrodes were implanted in the main knee and ankle flexor and extensor muscles of each hindlimb (lateral gastrocnemius, tibialis anterior, biceps femoris, and vastus lateralis). The electrodes were made of insulated stainless-steel Cooner AS632 wire. The bared recording site was 3–4 mm long and interelectrode spacing was 5–7 mm. The electrode leads were passed subcutaneously to the head where they terminated in a connector embedded in the acrylic headpiece.

Stimulation protocol. Starting 4 to 7 days following the surgery and twice a week thereafter, stimulation was applied through individual spinal cord microwires during testing sessions lasting up to 3 hours. Single-stimulus pulses (2/s, 300 μs, 10–240 μA) were delivered through each electrode individually and visual inspection, palpation, and intramuscular EMG recordings were used to determine the stimulus threshold and range over which individual muscles (e.g., tibialis anterior) or muscle groups (e.g., quadriceps or triceps surae) were activated in isolation (8, 9). Tetanic muscle contractions were obtained by delivering 50/s trains of 300-μs stimulus pulses varying in amplitude from 10 to 240 μA. Maximal stimulus strength was limited to 240 μA to avoid causing tissue damage (1).

EMG and torque measurements. EMG signals were bandpass filtered (30–3000 Hz), amplified by a factor of 4000, digitized at a rate of 11,000 samples per second, and saved on magnetic tape for later analysis. To measure knee extension and flexion torque, animals were anesthetized with sodium pentobarbital (1:5 saline dilution of the anesthetic delivered intravenously through a chronically implanted catheter in the jugular vein). The experimenter held the femur rigidly in place and a strain gauge (custom-made proving-ring transducer, compliance <0.01 mm/N) was placed distally around the shank, immediately above the ankle, through a noncompliant suture loop. The knee angle was held at 90° and so was the angle between the shank and the strain gauge. Isometric torque measurements were digitized at a rate of 11,000 samples per second and saved on tape.

Assessment of perception of stimuli. Cats were closely observed during their normal daily activities in the housing and laboratory areas. We looked for evidence of reduced appetite or refusal of food and water that might indicate a general malaise due to discomfort caused by the implants. During microstimulation, the animals either were seated in an experimenter's lap or stood quietly on a table. We looked for shifts of posture, vocalization or any other signs of orienting or avoidance behavior that would suggest that the spinal cord stimuli were uncomfortable. Food rewards were given from time to time to encourage the cats to stay in place. We looked carefully for pauses or cessation of eating behavior during microstimulation. A laser pointer was occasionally used to move a spot of light around the table surface as a distraction. Cats would watch this moving spot intently and occasionally made playful lunges toward it. Microstimulation was applied in short bursts to see if this play behavior was interrupted. We assumed that simple behaviors such as those described would be disrupted and replaced by orienting and avoidance behaviors if the stimuli involved strong and/or unpleasant sensations.

Determining the effect of afferent input on intraspinal stimulus threshold. In awake animals, intraspinal electrodes were independently activated at stimulus levels producing threshold EMG responses in one of the muscles of interest (e.g., quadriceps) and the activated muscle was stretched and shortened by manually imposing cyclical joint rotation. A gyroscope, placed midway between the knee and ankle on the ventral surface of the shank, was used to measure the angular velocity of the imposed movements. At least 50 consecutive 2/s pulses were delivered through each electrode individually during the imposed movements and the elicited EMG responses were recorded. EMG records were rectified after subtracting baseline activity (average activity during a 40-ms period immediately preceding the stimulus). Mean EMG activity within a 20-ms window starting 10 ms following a stimulus pulse was plotted against the instantaneous angular velocity measured 2 ms prior to the stimulus pulse. Since all electrodes showed a similar relationship between the elicited EMG activity and instantaneous angular velocity, the responses from all electrodes were pooled. The mean and standard error of EMG activity within 50°/s bins were calculated and the data were curve-fitted using a power-law relationship.

Determining the location of implanted electrodes. At the end of the experiment, animals were deeply anesthetized with sodium pentobarbital and perfused through the heart with a 3.7% formaldehyde solution. The lumbosacral portion of the spinal cord was removed with the wires in place. The spinal cord was then sectioned and the locations of the implanted microwires were determined.

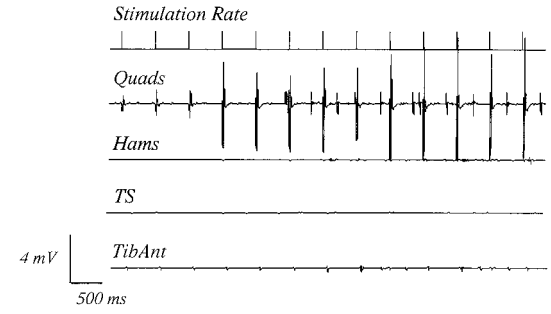

FIG. 2. EMG responses elicited by SCμstim. Responses obtained by stimulating one spinal cord microelectrode in an awake cat 3 weeks after implantation. The microelectrode stimulated the left side of the cord and selectively activated the quadriceps muscle group in the ipsilateral limb. Stimuli were 2/s, 300-μs-duration pulses, increasing in amplitude from 144 to 200 μA. The top trace serves as a stimulus event marker. (Quads, quadriceps; Hams, hamstrings; TS, triceps surae; TibAnt, tibialis anterior).

RESULTS

Responses Elicited by SCμstim

An example of the EMG activity recorded during pulsatile stimulation through one electrode in an awake cat is shown in Fig. 2. The electrode selectively activated the quadriceps muscle group. The selectivity of activation was maintained even at the highest stimulus level attempted (200 μA, 300-μs pulses) and very strong contractions were generated. There was no sign that the stimulation eliciting these contractions caused any discomfort. Activities such as feeding, grooming or watching a rapidly moving spot of light projected onto the floor from a laser pointer continued uninterrupted. In at least 67% of the electrodes activating quadriceps ($\geq$3 electrodes per animal), contractions elicited with stimulus pulse trains delivered through single electrodes generated knee extension torques up to 1 Nm. Note that a torque of about 0.6 Nm is required to support the hindquarters in stance. This estimate was determined from force and kinematic measurements obtained during stance.

Taken collectively, 60% of the implanted electrodes selectively activated individual muscles or small groups of muscle synergists producing movements about single joints throughout the duration of the experiments. Stimulation through 30% of the electrodes generated whole limb synergies with torques large enough to lift the animals' hindquarters. The final 10% of the implanted electrodes elicited cocontraction of several mutually antagonistic muscles resulting in stiffening of one or two joints without producing any net movement. Figure 3 shows examples of single-joint movements generated by stimulating individual electrodes in two different animals. Knee extension (Fig. 3A) and ankle dorsiflexion (Fig. 3B) were produced primarily due to the activation of quadri-

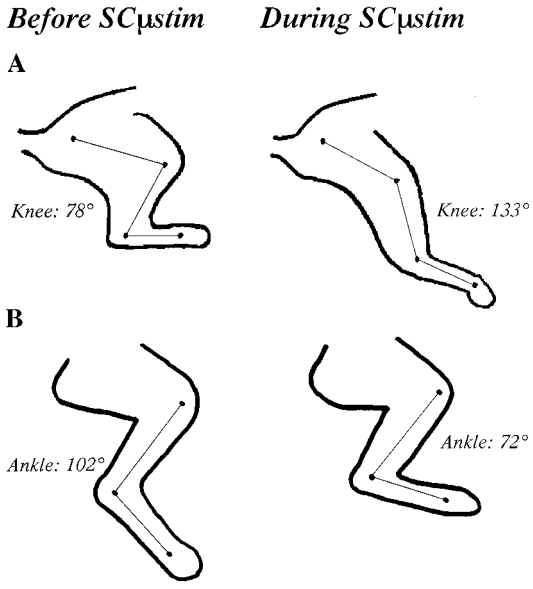

FIG. 3. Single-joint movements elicited by SCμstim in two different, awake animals. (A) An example of knee extension obtained by stimulating through a single electrode 1 month after implantation (50/s train, 300 μs, maximum amplitude of 144 μA). (B) An example of ankle dorsiflexion evoked by stimulating through a single electrode 1 month after implantation (50/s train, 300 μs, maximum amplitude of 200 μA).

ceps and tibialis anterior, respectively. Figure 4 demonstrates the hindlimb movements generated by stimulating through three different electrodes in an awake, weight-bearing animal. Stimulation through each electrode produced a powerful hip–knee–ankle extensor synergy without causing any apparent discomfort. The whole-limb extensor responses were primarily seen in animals in which the microwires were implanted within the caudal half of the lumbar enlargement (two of six animals). At least two or three electrodes on each side of the spinal cord evoked these powerful unilateral multijoint extensor synergies.

Across all animals, at least two-thirds of the implanted electrodes (range 67 to 100%, mean ± SD 80 ± 12.5%) consistently elicited contractions in the same muscle(s) throughout the period tested (Fig. 5A). For all electrodes, stimulus threshold doubled during the first 10 days following implantation. This was presumably due to electrode encapsulation, a product of the physiological reaction to implanted foreign objects. Following this initial increase, stimulus thresholds remained, on average, constant throughout the duration of implantation. Figure 5B describes the time course of change in stimulus threshold for all implanted electrodes in all animals. Average stimulus threshold at the time of implantation for all electrodes was 80 ± 10 μA (mean ± SEM). One week after implantation, the average stimulus threshold increased by 76%. It soon doubled, reaching an increase of 102% by the end of the first month, and remained fairly constant thereafter.

Figure 6 shows typical electrode locations determined during postmortem dissection and sectioning of the spinal cord which was performed in all cats. The electrode tips were primarily positioned in the ventral horn of the cord but about 25% reached into the ventral root exit zone. The evoked responses discussed above suggest that many of the electrodes were implanted in premotoneuronal and motoneuronal regions (5, 9, 14, 19).

Effect of Afferent Input on Stimulus Threshold

In nearly all electrodes, thresholds for activating muscles were lowered by palpating the muscles and their synergists, by imposing joint rotation that stretched the muscles or, in some cases, by lightly touching the skin over and around them. This reduction in threshold is presumably due to the depolarization of motor and premotor neurons by sensory input. Figure 7 shows the effect of imposed muscle stretch on stimulus threshold in an awake animal. Stimulation through an electrode activated the quadriceps muscle group. Imposed knee flexion increased EMG responses in quadriceps (i.e., the threshold for activating the muscle was reduced). Upon termination of knee flexion, evoked EMG activity returned to its prestretch levels. In order to

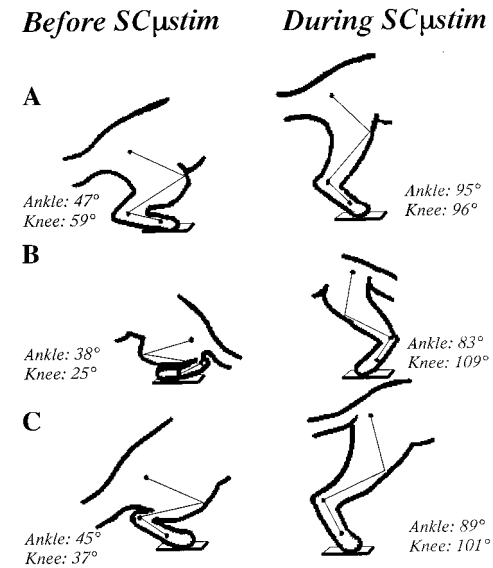

FIG. 4. Whole-limb synergies elicited by SCμstim. Shown are kinematic responses obtained by individually stimulating three spinal cord microelectrodes (A–C) in an awake, weight-bearing cat 2 months after implantation. Stimuli were 50/s trains of 300-μs pulses reaching a maximal amplitude of 240 μA. In all cases, microstimulation produced extensor torques capable of lifting the animal's hindquarters without any apparent pain or discomfort to the animal.

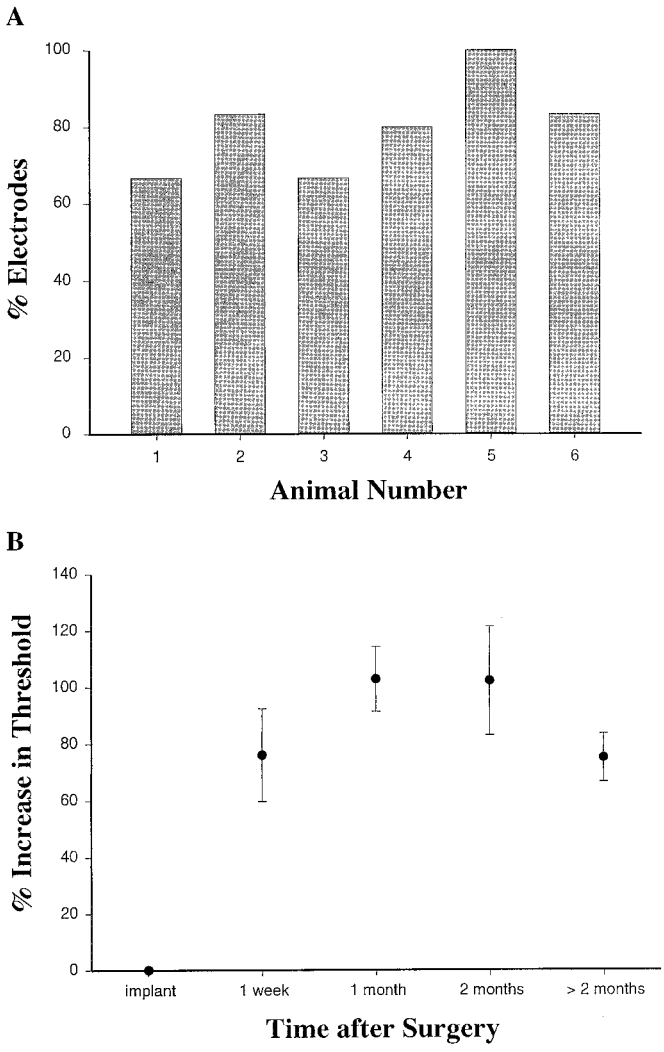

FIG. 5. Stability of evoked responses. (A) The percentage of electrodes activating the same muscle(s) throughout the duration of experiments in all animals is shown. At least two-thirds of the electrodes in all cats activated the same muscle(s) throughout the period after implantation (up to 6 months). (B) Mean ± SEM values describing the percentage of increase in stimulus threshold throughout the duration of implantation for all electrodes across all animals. At the time of implant stimulus threshold was 80 ± 10 μA (mean ± SEM). For all electrodes, stimulus threshold almost doubled 10 days after implantation but remained fairly constant thereafter.

quantify this effect we plotted the size of evoked EMG responses against velocity of imposed movement. Figure 8 shows quadriceps EMG responses obtained during imposed knee flexion in an awake animal. Six spinal cord microelectrodes were independently activated at stimulus levels producing threshold EMG responses in the stationary limb. Imposed knee flexion increased quadriceps EMG responses in a power-law relationship that is consistent with motoneuronal depolarization resulting largely from spindle Ia afferent input (12).

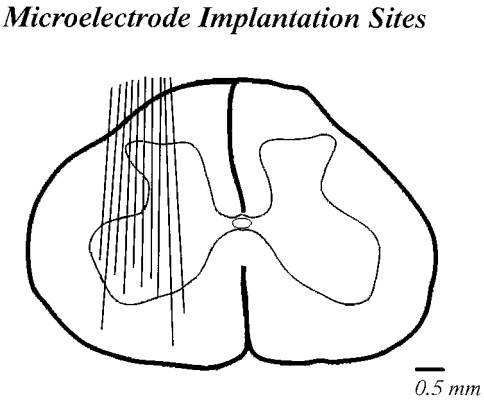

FIG. 6. Typical locations of implanted electrodes. Electrodes were targeted at the ventral horn of the spinal cord into regions containing motoneurons and premotoneurons. About 25% of the electrode tips reached into ventral root exit zones (three shown in this figure).

Lack of Obvious Functional Deficits

Implanted animals were maintained for up to 6 months. Throughout this time, no deficits were noticed in activities of daily life. Judging by the stability of evoked contractions and the gross histology, the electrodes remained fixed in place and caused no significant tissue damage even though the animals often

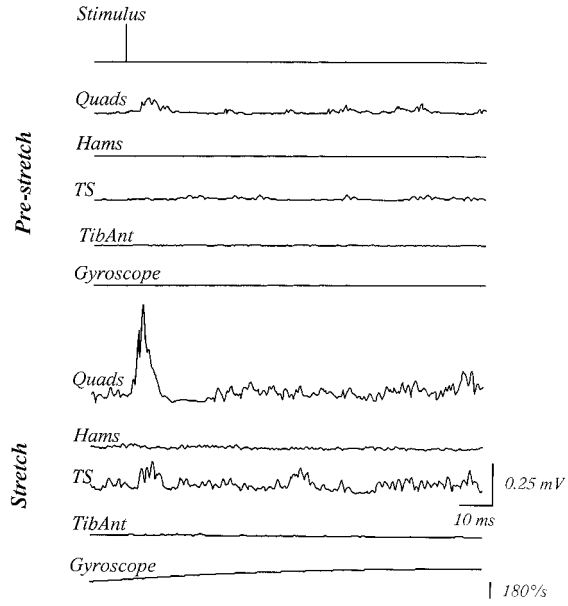

FIG. 7. Effect of afferent input on motor unit recruitment during SCμstim. Stimuli through one electrode in an awake animal were held at the threshold level for quadriceps responses. Imposed knee flexion increased quadriceps EMG responses. Upon termination of knee flexion, quadriceps EMG responses returned to their prestretch levels. Each EMG trace is the average of responses generated by 10 consecutive stimulus pulses. The gyroscope signal represents the angular velocity of imposed knee flexion. The slight increase in TS EMG activity during stretch may be due to the cutaneous input resulting from holding the leg.

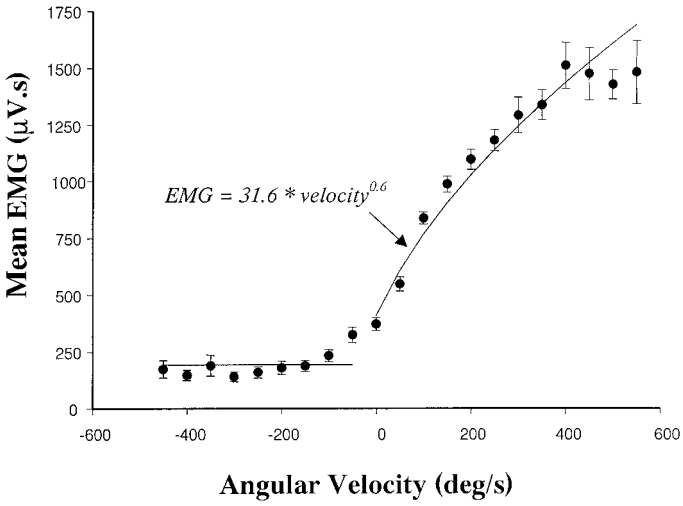

FIG. 8. Pooled quadriceps EMG responses during imposed knee flexion in an awake animal. Responses were obtained by independently stimulating six spinal cord microelectrodes [see Methods]. The mean and standard error of EMG activity within 50°/s angular velocity bins are shown. Phases of imposed knee flexion (positive angular velocities) were associated with increased quadriceps EMG responses (i.e., given the same stimulus level, EMG responses increased with increasing angular velocities of imposed movement). The horizontal line shows the mean integrated EMG activity during phases of imposed knee extension (muscle shortening). Curve-fitting was performed for positive velocities only, as the stimuli were just suprathreshold for zero velocity. The fitted curve indicates a power-law relationship with an exponent of 0.6 ($r = 0.98$, $P < 0.0001$).

jumped and frolicked around the laboratory or housing area. Gross examination of the spinal cord upon termination of the experiment showed mild thickening of the dura mater on the dorsal surface of the cord immediately above the implanted region in two animals. In the remaining animals, the spinal cord looked normal.

In two animals, paresis in one hindlimb lasting a few days was unintentionally caused during surgical dissection rostral to the electrode implant site. Microstimulation-evoked responses in the affected limb were similar before and after the resolution of paresis over the course of 2 weeks.

DISCUSSION

Intraspinal microstimulation is a novel approach to restoring mobility in paraplegia. It is based on stimulating muscles by tapping into their control centers in the spinal cord. Prior to our study there were serious doubts as to whether long-term stability of implanted microwires could be achieved. For example, chronic SCμstim for bladder control was recently attempted in cats but problems with electrode fixation and stability were encountered (2). However, our results demonstrate that, with suitable fixation techniques, spinal cord microwires remain securely in place and muscle responses remain stable for long periods of time (Fig. 5). From a basic science perspective, our chronic implantation technique makes it possible to study the motor effects of activity evoked in specific regions of the spinal cord in awake, behaving animals.

The lack of obvious functional deficits throughout the duration of the experiments suggests that the implanted microwires were not physically damaging the spinal cord. It also suggests that the overall tissue disruption and displacement by the implanted electrodes was minimal. It is therefore anticipated that complications due to the fixation of electrodes in the spinal cord of paralyzed humans who are much less physically active than the animals in this study would be minimal. Previous studies of chronically implanted microwires in cats indicated that the cellular damage in the spinal cord was limited and localized (21).

With relatively low stimulus levels, intraspinal microstimulation produced strong activations of single muscles or muscle synergies in the conscious animal without causing apparent discomfort (Fig. 3). Some electrodes elicited joint torques sufficient to support the animals' hindquarters (Fig. 4). Given the shape of motoneuron pools in the ventral horn of the lumbosacral spinal cord (on average, motoneuron pools are <1 mm in diameter and $\sim$10 mm in length (7, 19)), the selective and powerful activation of limb muscles may not be solely due to the direct activation of motoneurons. It may also be the result of activation of premotoneurons which in turn activate motoneurons along the length of a pool. Henneman's finding that the interneuron to motoneuron ratio in motoneuron pools is seven to one lends support to this argument (6). By producing distributed activation of motoneurons throughout their pool, focal SCμstim could bring about a more physiological recruitment pattern of motoneurons. In addition, previous acute experiments demonstrated that the smoothness of muscle contractions and resistance to fatigue are significantly improved by interleaving the stimuli between electrodes eliciting similar mechanical actions (7, 13, 22). Whole limb synergies may arise from focal stimulation of premotoneuronal areas in the spinal cord (5) or the activation of regions of overlapping motoneurons within the caudal portion of the lumbar enlargement (19). Several electrodes implanted on both sides of the spinal cord individually generated unilateral synergies similar to the ones shown in Fig. 4. Therefore, patterned stimulation through as few as two or three electrodes could restore simple functional activities such as maintaining a standing posture.

The high proportion of electrodes producing selective muscle activation in the awake cat reaffirms previous results in acute studies (8, 9) and provides the means for designing flexible control strategies which allow for the generation of novel and functional movements. Combined with the whole limb movements seen when stimulating through one-third of the electrodes, a large

repertoire of stereotypical and novel movements could be generated using intraspinal microstimulation.

Our data demonstrated that stimulus thresholds were affected by afferent input (Figs. 7 and 8). In designing neuroprostheses, it will be important to take these results into account, as they suggest that the input/output characteristics of the activated muscles may be continually modulated through sensory feedback generated during movement. Therefore, a knowledge of the relationship between sensory input and the reduction of stimulus threshold could be valuable for choosing proper stimulation protocols in which the stimulus levels are continuously modulated based on sensory input from the target muscles.

Preliminary qualitative observations indicated that stimulus thresholds were also reduced during voluntary contractions of muscles. If these observations are confirmed, SCμstim may have further important clinical implications. By providing steady stimulation through implanted electrodes, weak voluntary activations of one or more muscles could be selectively enhanced. This could be useful for retraining of voluntary muscle control in people with incomplete lesions, who have some residual or even subliminal control over motoneuron pools.

More than a decade ago, Seligman suggested that an ideal neuroprosthesis would utilize thousands of spinal cord microelectrodes placed at critical locations in order to elicit (spatially and temporally) selective muscle contractions (15). Our results suggest that microelectrodes placed at a dozen locations may be all that is needed to restore simple functional movements such as standing and stepping in paraplegia or grasping a cup in quadriplegia. The technique could further be extended to applications including control of bowel and bladder, respiration, and sexual function. It could also be used for promoting secretion of neurotrophic factors (17) and for enhancing regeneration through implanted tissue grafts in the central nervous system.

A discussion regarding the use of electrical stimulation for activating spinal cord networks controlling locomotion, balance, and posture following spinal cord injury has recently been published (4). It was envisioned that electrical stimulation could be used for enhancing specific spinal reflexes during the step cycle to facilitate the activation of extensor muscles, stimulating multiple spinal cord tracts to initiate a locomotor pattern, or activating various networks within a central pattern generator to produce functional muscle synergies. Our study provides the crucial evidence that an implanted system of microwires would be viable in the long term. It therefore supports these speculations by providing the first concrete indication that SCμstim may be feasible for restoring mobility in spinal cord injured humans. However, other than evoking whole-limb synergies when independently stimulating through one-third of the implanted microwires, our results, to date, show no evidence that microstimulation through electrodes implanted in nonsensory areas in the cord generates rhythmic movements similar to those produced by central pattern generators. This may indicate that focal stimulation through a single electrode in premotor and motoneuronal areas is inadequate for activating an entire central pattern-generating network. Furthermore, given that the spinal cord was intact in all animals, the lack of evidence for rhythmic movement generation with ventral SCμstim may also indicate that the independence and function of a central pattern generator may be significantly altered in the presence of any descending drive. On the other hand, rhythmic paw-shake movements were seen in one animal when stimulating through single electrodes intentionally implanted dorsally in the cord. However, since the animal consistently reacted by licking the dorsum of its foot following the paw-shake movements indicating the involvement of higher level sensory systems, this rhythmic behavior was not necessarily due to direct activation of a paw-shake pattern generator located in the spinal cord.

The observation that SCμstim does not cause apparent discomfort in the intact animal even when powerful muscle contractions are evoked is very important for any future clinical application of the work. It implies that pain pathways are not activated, thus removing a potential barrier to clinical implementation and acceptance by patients. Moreover, the observation that SCμstim-evoked responses were similar before and after the resolution of paresis in two animals suggests that functional muscle contractions can be elicited by microstimulation not just of the normal spinal cord, but also in individuals after spinal cord injury rostral to the electrodes. Thus, taken collectively, the results demonstrate that SCμstim could be a useful clinical approach for restoring functional movements in paraplegia and quadriplegia. With spinal column laminectomies now a common practice following spinal cord injury, implanting the necessary microwires in the spinal cord would be a relatively minor addition to the surgical procedure.

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