Efficacy of Intraspinal Microstimulation in Restoring Stepping after Spinal Cord Injury

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Abstract

The goal of this project was to test the efficacy of intraspinal microstimulation (ISMS) in restoring leg movements after spinal cord injury (SCI). Three aspects of ISMS-generated movements were tested: 1) kinematics and kinetics of evoked stepping, 2) fatigue resistance and muscle fiber-type recruitment, and 3) long-term stability of stimulation parameters and elicited responses. Studies were conducted in cats with long-term SCI and intact rats. ISMS evoked near-normal stepping that was fully weight-bearing and fatigue resistant in paralyzed cats. More than 60% of muscle fibers activated with ISMS in rats were slow and fast, fatigue-resistant. In contrast, 85% of fibers activated with epineural stimulation through cuff electrodes were fast, fatiguable. In one cat with SCI, ISMS microwires were implanted for 6 months. Stimulus threshold remained constant throughout the period of implantation. Hind limb responses were dominated by flexor contractions over the first 8 weeks post-injury, during which spinal shock and hyperreflexia were manifest. In the proceeding 4 months, ISMS evoked a full repertoire of stable and predictable limb movements. The findings suggest that ISMS may be a viable electrical stimulation approach for restoring leg movements after SCI.

1 Introduction

Intraspinal microstimulation was suggested as a potential functional electrical stimulation (FES) technique for restoring standing and walking after SCI [1]. The lumbar enlargement, which is 5 cm-long in humans, is the target region for implantation. This region contains motoneurons innervating all lower extremity muscles as well as a large proportion of the neuronal networks involved in locomotion. By tapping into this “control center” in the cord, one can take advantage of built-in networks which generate synergistic leg movements.

We previously demonstrated that ISMS microwires chronically implanted in intact cats remain securely in place throughout the period of implantation [2]. Stimulation thresholds, ranging between 2-30 µA in amplitude, doubled over the first 4 weeks post implantation, presumably due to natural encapsulation processes, and remained constant thereafter. Stimulation through at least 67% of the microwires in each animal continued to elicit consistent limb movements [2]. These findings highlighted the feasibility of ISMS as a potential FES approach. The present preliminary studies investigated the efficacy of ISMS in restoring stepping after complete SCI. Three separate studies were conducted concurrently to test 1) the capacity of ISMS to restore functional stepping after chronic SCI, 2) the fatigue resistance of evoked stepping and muscle fiber-type recruitment, and 3) the long-term stability of ISMS parameters and elicited responses after SCI.

2 Methods

Experimental protocols were approved by Univ. Alberta Animal Welfare Committee.

2.1 ISMS-evoked stepping after SCI

Adult cats (n=4) were spinalized at T11, using aseptic surgical techniques. Buprenorphine was administered 3x per day for 2-3 days to ensure comfortable recovery. Bladders were manually expressed twice daily and muscles of the hind limbs were stretched. Two to four weeks later, acute experiments were conducted during which microwires were implanted bilaterally in the lumbar enlargement under isofurane anesthesia. Microwire implantation followed published techniques [2, 3] and targeted regions of the ventral horn that generate hip, knee, and ankle flexor or extensor movements when electrically stimulated [4]. The cats were then
decrebrated and anesthesia terminated. The animals were transferred to a custom-built split belt treadmill with indwelling force plates, and placed in a body harness that provided partial body weight support. The treadmill belts remained stationary throughout the course of experiments. Reflective markers were placed on the main joints of both limbs, and movements were recorded using digital camcorders. Electrical stimuli (1s trains, biphasic, charge balanced pulses, 200 µs, 2-300 µA, 40 or 50 s⁻¹) were delivered through individual microwires and those eliciting flexor, extensor, forward or backward movements were identified. Bilateral stepping was generated by simultaneously delivering interleaved, amplitude-modulated stimuli through wires in one side of the cord eliciting whole-limb extension and wires in the other side eliciting whole-limb flexion [3, 4]. Kinematics, kinetics and electromyographic activity of the evoked stepping were documented.

2.2 Type identification of muscle fibers activated by ISMS

Previous experiments suggested that ISMS recruits motor units in near-normal physiological order [5]. In the present study, muscle fibers activated by ISMS were directly identified by inspection of their glycogen content. Acute experiments were conducted in two groups of adult rats. Under isoflurane anesthesia, one group (n=6) received ISMS in the region of the cord activating the quadriceps muscle group. Epineural stimulation of the femoral nerve using cuff electrodes was used to activate quadriceps in the second group (n=6). In both groups, stimuli were delivered in 4, 5 min bouts separated by 1 min of rest. The animals were then euthanized and quadriceps removed from both hind limbs and frozen. Vastus lateralis (VL) and rectus femoris (RF) were subsequently sectioned and stained for glycogen. Immunohistochemistry for myosin heavy chain was used to identify the fiber-types in VL and RF and match them with those showing glycogen depletion.

2.3 Long-term Stability of ISMS-evoked Responses after Chronic SCI

To test the stability of ISMS parameters and evoked responses after chronic SCI, one cat was spinalized at T11, implanted with ISMS microwires, and maintained for 6 months postsurgery. The purpose of this preliminary study was to assess the changes in neuronal networks after SCI and determine their capacity to evoke functional movements when activated with ISMS. Twice a week, stimulus threshold and evoked responses were obtained for each wire. Changes in these measures were documented throughout the implantation period.

3 Results

3.1 ISMS-evoked stepping after SCI

Synergistic multi-joint movements of the hind limbs in cats with complete SCI were generated by ISMS through individual microwires. Average stimulus threshold (Th) across all animals and all microwires was ~30 µA. Amplitude-modulated (Th - 4 or 5x Th), phasic ISMS through 4 microwires in each side of the spinal cord generated near-normal bilateral stepping. Stimuli were interleaved between microwires producing similar mechanical action [1, 4]. Full weight-bearing during stance and ample foot clearance during swing were achieved. Moreover, the evoked stepping appeared to be fatigue resistant (Figure 1).

Figure 1: Fatigue-resistant stepping evoked by ISMS. Shown is the equivalent of stepping for 200 m in man.

3.2 Type identification of muscle fibers activated by ISMS

Interleaved ISMS accounts for the significant fatigue resistance seen in the evoked stepping [1, 4]. However, in addition to the advantage of reducing stimulus frequency with interleaved ISMS, ISMS appeared to inherently activate motor units in near-normal physiological order [5]. This was confirmed in the present study in which direct identification of muscle fibers activated by ISMS was employed. More than 60% of VL fibers activated by ISMS were slow and fast, fatigue resistant (type I and IIA, respectively). In contrast, less than 15% of fibers activated by stimulation of the femoral nerve through cuff electrodes were type I and IIA. The same trend was observed with near-Th stimulation as well as with 3x Th.
3.3 Long-term Stability of ISMS-evoked Responses after Chronic SCI

Figure 2 shows the stimulus thresholds in one animal with chronic SCI and ISMS implant. The measurements were obtained over a 6-month period and normalized to the first value measured post-surgery. Stimulus threshold remained constant throughout the period of implantation. Flexion withdrawal dominated the responses evoked by ISMS during the first 8 weeks post-surgery, the period during which spinal shock and flexor hyperreflexia of the hind limbs were strongly manifest. ISMS evoked a wide range of hind limb movements post the spinal shock period, which comprised of strong extensor, forward, backward and flexor synergies. Single joint movements were also obtained. All evoked movements remained constant in the ensuing 4 months.

![Figure 2: Stimulus thresholds for 24 microwires implanted for 6 months in a cat with SCI.](image)

4 Discussion and Conclusions

We conducted a set of preliminary studies to investigate the efficacy of ISMS in restoring leg function after SCI. These experiments were the first to directly address the viability of ISMS as an FES approach after SCI. The findings to date suggest that the neuronal networks for locomotion continue to be viable after SCI, and that ISMS could indeed restore functional stepping after injury, evoke weight-bearing fatigue resistant movements and recruit motor units in near-normal physiological order. Moreover, ISMS continues to elicit stable and predictable limb movements months after SCI. Activation of whole-limb muscle synergies, fatigue resistance, and near-normal order of motor unit recruitment suggest that ISMS operates through distinctively different mechanisms than those utilized in peripheral FES. ISMS through individual microwires acts as a point source, which activates all neural elements close to the microwire tip. This would include motoneurons, interneurons and fibers in passage. In fact, a recent study demonstrated that ISMS activates afferent fibers at lower stimulus levels than those needed for direct activation of motoneurons [6]. This “network activation” is very likely responsible for the coordinated, multi-joint muscle synergies evoked by ISMS through the majority of microwires implanted in the ventral horn. Furthermore, the networks activated in the ventral horn are characteristically different from those activated by ISMS in the intermediate or dorsal regions of the grey matter. Stimulation in the latter regions exclusively produces flexor withdrawal responses, presumably due the activation of cutaneous and pain afferent endings. Stimulation in the ventral horn is likely to activate proprioceptive afferent endings more selectively, thereby eliciting a wide range of synergistic movements. Finally, activation of interneurons and proprioceptive afferent endings contributes significantly to the near-normal recruitment of motor units with ISMS, given that afferents activate motoneurons in their correct size order.

In conclusion, the results of these preliminary studies collectively support the hypothesis that ISMS may be an efficient FES approach for restoring standing and walking after SCI.

References


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