Understanding the Mechanisms and Sites of Action of Intraspinal Microstimulation

Calixto R and Mushahwar VK

Department of Cell Biology and Centre for Neuroscience, Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

Vivian.mushahwar@ualberta.ca

Abstract

The goal of this study was to examine the sites of action of intraspinal microstimulation (ISMS) in the lumbosacral spinal cord. ISMS is a functional electrical stimulation (FES) approach currently under development for restoring standing and walking after spinal cord injury (SCI). Responses evoked by ISMS include graded single joint movements and coordinated multi-joint synergies. The evoked responses are fatigue-resistant and the activated motor units are recruited in a near normal physiological order. These responses vary significantly from those obtained by peripheral FES and suggest that ISMS activates motoneurons (MNs) indirectly, or trans-synaptically. Experiments were conducted in adult cats to address this question. We investigated whether ISMS activates fibers in passage including afferent projections and propriospinal neurons in addition to its direct activation of MNs. Extracellular single cell recordings were obtained during ISMS from cells distributed throughout the lumbosacral enlargement in animals with intact afferent projections and deafferented animals, and the effect of ISMS on the firing rate of the recorded cells was determined. Nearly 1/2 and 1/3 of the cells recorded in intact and deafferented animals, respectively, experienced changes in their firing rate in response to ISMS. These cells were located up to 10 mm away from the ISMS microwire tips. These results demonstrate that in addition to activating MNs directly, ISMS activates fiber in passage systems that are in turn responsible for the range of responses evoked by ISMS.

1. INTRODUCTION

Intraspinal microstimulation (ISMS) is a novel functional electrical stimulation (FES) technique for restoring standing and stepping after spinal cord injury (SCI). It entails the implantation of ultrafine wires in the lumbosacral enlargement of the cord with tips targeting the ventral horn. The lumbosacral enlargement is a small region of the cord, spanning 5 cm in humans (3 cm in cats). It contains the cell bodies of motoneurons (MNs) innervating all the muscles of the lower extremities, as well as large proportions of the neuronal networks involved in the coordination of leg movements, such as standing and locomotion.

We have shown that ISMS generates single joint movements and coordinated multi-joint synergies in intact animals [1-4] as well as in animals with complete SCI [5,6]. Stimulation through as few as 4 microwires in each side of the cord produces long durations of weight-bearing standing [7]. Furthermore, stimulation through as few as 4 microwires in each side of the cord in animals with complete SCI produces weight-bearing, kinematically stable of the paralyzed hindlimbs [5,6]. These findings were unanticipated given the complexity of the locomotor networks within the spinal cord. We also showed that ISMS recruits motor units in a near-normal order according to their size [8], resulting in the generation of graded muscle force [4,8,9]. The near-normal recruitment of motor units accounted in part for the fatigue-resistant contractions produced by ISMS.

These exciting results raised questions regarding the mechanisms and sites of action of ISMS. We specifically asked: How does the focally applied ISMS recruit distally located MN pools to produce multi-joint synergies and locomotor rhythms? Moreover, how does ISMS activate motor units in a near-normal order? We hypothesized that in addition to direct activation of MNs in the vicinity of the microwire tips, ISMS activates axons in passage composed of projections of afferent fibers in the ventral horn as well as propriospinal neurons. Activation of these axons leads to indirect, or trans-synaptic,
activation of relevant MN pools, which in turn recruits MNs in the correct physiological order.

2. METHODS

To test these hypotheses, we obtained extracellular recordings from cells located throughout the lumbosacral enlargement during ISMS in adult cats (n=9). All animal protocols were approved by the Univ. Alberta Animal Care Committee. Animals were anesthetized with isoflurane and a laminectomy was performed to expose spinal cord segments L4-S1. The animals were then placed in a standard stereotaxic unit and 6 or 10 microwires (30 µm stainless steel, insulated except for 30-60 µm at the tip) spaced 3 or 2 mm apart, respectively, were implanted in one side of the cord, with the tips placed in the ventral horn. The animals were then decerebrated at the intercollicular level and anesthesia was terminated. Six (6) of the animals had intact afferent projections. In three (3) animals, the lumbosacral enlargement was deafferented through a dorsal root rhizotomy conducted ~4 wks earlier. Intact and deafferented animals were used to determine the differential effect of ISMS on the afferent and propriospinal systems of the spinal cord.

Extracellular single unit recordings were processed offline. Following removal of the ISMS stimulus artefact, single cell potentials were discriminated and their spontaneous instantaneous firing rate was calculated. The effect of ISMS on the firing rate of the cells was then determined and characterized as short-latency excitation (SLE), short-latency inhibition (SLI), delayed excitation (DE) or delayed inhibition (DI) depending on the latency between the change in firing rate and stimulus onset as determined from post-stimulus time histograms. The dorso-ventral, medio-lateral and rostro-caudal location of these cells relative to the microwire tips was then identified.

3. RESULTS

In animals with intact afferent input, unitary recordings were obtained from 106 cells (width of potential >0.5 ms) and 25 axons (width of potential < 0.5 ms). Of the cells recorded, 47% showed changes in the firing rate during ISMS, of which, 90% experienced increases in their firing rate and 10% decreases in firing rate. The axons responding to ISMS had a similar laminar distribution to that of the cells responding to ISMS.

In total, 22 cells were recorded in the deafferented animals. Compared to the intact animals, fewer spontaneously active cells were encountered in the lumbosacral enlargement. Nonetheless, 38% of the recorded cells responded to ISMS. Of these, 67% showed increases and 33% decreases in firing rate. The cells were also primarily located in laminae VII-IX and were distributed rostro-caudally 1.0–6.0 mm away from the microwire tip.

4. DISCUSSION AND CONCLUSIONS

The results confirmed that in addition to activating directly MNs close to the microwire tips, the effect of ISMS is amplified by the activation of afferent and propriospinal projections. These projections coordinate the activation of synergistic MN pools; therefore, by stimulating them, ISMS is capable of producing coordinated, multi-joint synergies and rhythmic locomotor-like patterns with only few microwires in the cord.

More specifically, due to the proprioceptive, propriospinal and other interneuronal connections between synergistic MN pools within the ventral horn [10,11], ISMS of one MN pool also results in the activation of these fiber in passage systems, which in turn leads to the activation of coordinated whole-limb synergies [1,2,6,7]. For example, collaterals from a single Ia afferent fiber form synaptic connections with every MN within the homonymous pool as well as connections with MNs in synergistic pools [10,12]. Collaterals of all proprioceptive afferents producing patterns of synaptic excitation and inhibition of agonist and antagonist pools are also present in the ventral horn [10]. Furthermore, propriospinal interneurons which interconnect synergistic lumbosacral MN pools separated 1–3 cm rostro-caudally are located within the ventral horn, and the initial segments of their axons would constitute part of the fiber in passage systems activated by ISMS [11, 13]. Thus, the network of fibers in passage, which interconnects the MN pools and is directly related to the generation of limb movements, is contained within the ventral horn, the location of the ISMS implant.
Previous studies demonstrated that extracellular stimulation within the spinal cord activates fibers in passage at lower stimulus intensities than neuronal cell bodies [14-18]. Fibers in passage in the ventral horn are most likely composed of the axonal projections of afferent axons, propriospinal neurons and other interneurons. Activation of these fibers by ISMS leads to the amplification of the locally applied ISMS, full recruitment of MN pools, and the full recruitment of the muscles they innervate. Moreover, activation of fibers in passage produces trans-synaptic activation of MNs, which results in an orderly recruitment of the MNs according to their size, starting with small fatigue-resistant ones at low stimulation intensities [12, 19, 20]. Direct activation of MNs does occur at higher stimulus intensities in which the neurons are recruited in a reversed order. Thus, ISMS recruits motor units in a mixed or near normal order according to their size as opposed to the reversed recruitment commonly seen with peripheral forms of FES.

These findings extend our understanding of the mechanisms of action of ISMS. They also have significant implications to other central stimulation approaches such as epidural stimulation and deep brain stimulation.

References

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