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Epidural stimulation of the spinal cord in spinal cord injury: current status and future challenges

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A spinal cord injury can occur at any point along its length and can have a wide range of severities and varying effects on sensory and motor function, depending largely on these two factors. While considerable function can be recovered if the injury is ‘incomplete’ – that is, there remain some functional connections between the brain and the spinal cord segments below the lesion – there has been little success in improving function after a motor and/or sensory complete lesion. Recently reported functional gains in an individual with complete motor paralysis was possible because most of the cellular structure below the lesion remains intact [1]. It is this network of neurons that can actually control very complicated movements when this spinal network (not the brain itself) receives the appropriate sensory input, and when the excitability of this network is enhanced with a very specific pattern of modest levels of stimulation with epidurally placed electrodes. We refer to this intervention as electro-enabling motor control.

Based on extensive animal experimentation of this spinal network, the possibility of regaining locomotor function after complete paralysis in human subjects becomes an important issue. To begin to examine this issue, we performed similar experiments in a single subject with complete motor paralysis. The issues are: is the human spinal cord circuitry without any input from the brain as smart as that of the rat or cat, can it be neuromodulated to stand and to step using epidural stimulation as demonstrated successfully in the rat and cat, and can proprioception serve as a source of control of the spinal circuitry? We made a series of observations demonstrating the feasibility of using epidural stimulation to facilitate the recovery of a series of consciously controlled motor functions, as well as other functions, some of which are largely considered to be autonomically controlled. After implanting an electrode array, recovery of several functions occurred following repeated sessions of epidural stimulation and training to stand and to step, and to exert voluntary control of the lower limbs. The subject is a 23-year-old man with paraplegia from a C7–T1

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subluxation as a result of a motor vehicle accident who has had a complete loss of clinically detectable voluntary motor function and partial preservation of sensation below the T1 cord segment. After 170 locomotor training sessions over 26 months, a 16-electrode array was surgically placed on the dura (L1–S1 cord segments). The results from this single subject provide a wakeup call for a change in the perception of the potential for recovery of function using activity-dependent interventions [2]. They also highlight the potential advantage of quantitative assessment of multiple parameters in fewer individuals in lieu of the commonly accepted ‘primary outcome’ measure, often with limited objectivity, in many subjects.

Current status

Our observations in the 18 months following the implant have provided the ‘proof of principle’ that epidural stimulation of the spinal cord can be used to enable an individual with motor complete paralysis of the lower limbs to use the propriospinal input derived from the muscles, bones and skin that are projected to the lumbosacral spinal cord circuitry and can serve as a source of neural control [1]. This neural control, driven by the sensations derived from the kinetic and kinematic events associated with standing and stepping, demonstrates that the neural circuitry of the human spinal cord has remarkable similarities qualitatively to those that have been observed in rats [3] and cats [4] that have recovered full weightbearing stepping after a complete spinal cord transection. Although the implantable device used for epidural stimulation was designed largely as an intervention to suppress pain, the existing, but limited, technical properties were sufficient to enable the recovery of significant gains in motor function. These results question a number of commonly held assumptions about spinal cord injury and the potential for functional recovery, and expose new avenues that can lead to the recovery of function.

The specific and more important changes that we observed were as follows: first, recovery of active control of full (100%) weightbearing, independent standing for several bouts of up to 15–20 continuous min within an hour training session. Some active postural control capability by the spinal neural circuitry was evident when the subject was exposed to different loads and changes in center of gravity during these training sessions. The ability to stand for short periods occurred within a matter of weeks of the implant, but the ability to stand continues to improve even now, 1–1.5 years postimplant, as he continues to practice standing. Second, rhythmic stepping patterns could be generated in the presence of epidural stimulation, although the coordination was not sufficient to accomplish full weightbearing independent stepping. Three, voluntary control of bladder function was recovered. Four, a more normalized blood pressure control was reestablished. Five, significant improvement in body temperature control was attained. Six, improvement in sexual function was reported. Seven, muscle mass increased substantially. But in addition to these multisystem-level functional improvements, after 6–7 months of primarily stand training, conscious, voluntary control of both lower legs was recovered to the point that while lying supine, the legs can be flexed repeatedly to the point that the knee reaches a 90° angle and individual joints can be selectively controlled. This voluntary control can only be manifested in the presence of epidural stimulation, as was always true of standing and stepping. Voluntary control of the bladder began to occur several months postimplant, even without the simultaneous presence of stimulation. The dependence of each of these variables on training and the specificity of training remains to be determined.

Implications of observations

Several points are important to emphasize. First, remarkable levels and kinds of recovery of neuromotor functions can occur years after a severe spinal cord injury. Second, all of these changes were probably dependent on the fact that the epidural stimulation was administered

in synchrony with stand and step training and, eventually, training the voluntary control efforts. Relative to the animal experiments that provided the primary rationale for the human implant, we have not yet even attempted to incorporate pharmacological neuromodulation in conjunction with epidural stimulation and training as was so successful in rats [5]. Third, it became evident rather quickly when examining different stimulation patterns in the human experiments that the technical limitations of the implanted device was severely restrictive relative to what was needed to manifest the maximum potential of the spinal circuitry to generate standing and stepping. Fourth, the recovery of voluntary control of the lower limbs and the presence of epidural stimulation obviously raises an important question as to what the specific supraspinal and spinal mechanisms were that could account for this new supraspinal control. This observation elevates the urgency of developing detailed neurophysiological and imaging assessments of, not only the human subjects, but also developing an appropriate animal model whereby the different experimental variables can be isolated in detail. These studies are likely to determine which individuals with a given clinical diagnosis are likely to benefit, and how much, from one or more of these interventions.

These observations highlight another long-standing issue as to the nature of a motor complete injury. Some evidence suggests that most of the individuals with clinically motor complete paralysis do not have a complete anatomical separation of the proximal and distal ends of the spinal cord at the site of the lesion [6]. The absence of a clear functional dichotomy of a spinally complete and incomplete injury has been demonstrated to be dependent on the thoroughness and procedures of the clinical examination. For example, in individuals that are considered to be motor complete based on a standard clinical assessment, a more detailed assessment can reveal some residual motor function [7]. Thus, from a functional perspective, there are probably gradations of completeness of the injury that can easily remain undetected. Could remaining descending axons that cross the lesion be 'reawakened', and if so, what is the mechanism? Such a scenario would emphasize the importance of there being some remaining anatomical continuity of axons across the lesion, even though they may have no remaining functionally detectable synaptic function before the epidural stimulation began. On the other hand, they could have some remaining function, but the magnitude of the synaptic events that remain may be insufficient to be manifested in any recognizable clinical assessment. Perhaps, when voluntary control was recovered in the presence of stimulation, the epidural stimulation modulated the circuitry to a higher level of excitability, which allowed for some residual descending motor input to exceed the motor threshold of some motor neurons. However, even if this was the case there had to be some fundamental reorganization of the supraspinal and/or spinal circuitry that occurred after months of stimulation and training. Or was the recovery of voluntary control attributable to a combination of stimulation and repeated voluntary efforts generated simultaneously that induced axons to grow through or around the lesion and make functional connections in the proximal stump? If this did occur, then a remarkable ability of the descending axons to form functional connections to interneurons (probably propriospinal neurons) that can then generate coordinated movements is rather impressive and certainly encouraging.

Future challenges

As it currently stands, the rate at which we can significantly improve levels and kinds of recovery is simply a function of how rapidly we can tackle the following challenges: first, develop a stimulating device that has sufficient flexibility and control of the parameters needed to fine-tune motor responses. Second, develop machine-learning algorithms that will provide the capability to rapidly identify the appropriate stimulation parameters to achieve a given motor response in a given individual with a given injury at a given time in their postinjury period. Third, develop electrode arrays that can take advantage of the localization

of select clusters of interneurons that control specific motor pools and their respective muscles. Fourth, develop a brain–machine–spinal cord interface that can be controlled by the subject to select and fine-tune all motor responses online. Fifth, develop robotic devices that can provide useful, real-time feedback on performance, as well as design robotics that function more effectively as a more integrated component of the biological systems that are being controlled and trained. Six, determine whether these interventions could be useful in improving neuromotor performance following movement disorders having different origins. Seven, develop rehabilitative devices that can be used at home so that interventions can be incorporated into one's daily life.

In summary, the viewpoint that little can be done to improve motor function after spinal cord injury, that the rehabilitative efforts needed to regain function are too time-consuming and expensive, that the gains are too small to be clinically important, and that biological bases of recovery in animal models of motor dysfunctions have minimal or no relevance to humans, all seem conceptually and scientifically part of the past, not the present. It is time to revisit the assumption that progress toward developing clinically effective treatments (which in some circles has come to mean 'evidence-based medicine') must follow a single path and procedure that includes identifying a single primary clinical outcome measure (which is often semiquantitative at best) to represent intervention effectiveness and that data only derived from a double-blind design can be used as evidence. Perhaps a thorough and quantitative assessment of multiple parameters of a highly integrative system, such as the human in real life conditions, would be more enlightening than a soft measure of one parameter on a large number of patients, at least in the earlier phase of establishing 'clinical effectiveness'. The *Lancet* article serves as an example [1]. With such multisystem changes, how can one select a primary outcome from the multiple and highly significant observations made on this one individual?

Returning to the biological issues on which the recent study was based, yes, the human spinal cord is smart and it can use proprioception as a source of control and epidural stimulation can serve as an effective way to access this circuitry. Now that the proof of principle is rather evident even when based on a single subject, the results highlight a series of challenges that, if met, are likely to eventually result in a paradigm shift in our expectations and realizations of the level and kinds of recovery that can occur with a highly integrated and carefully developed rehabilitative strategy.

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Biographies

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